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## Long-Term Follow-up of Very Preterm Infants

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### ABSTRACT & COMMENTARY

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**Synopsis:** Individuals who were born very preterm (< 32 weeks) had higher rates of neurocognitive and behavioral problems than controls when studied in adolescence. More brain lesions were demonstrated by MRI than had been noted by neonatal cerebral ultrasonography.

**Source:** Stewart AL, et al. Brain structure and neurocognitive and behavioral function in adolescents who were born very premature. *Lancet* 1999;353:1653-1657.

Infants who are born very prematurely (< 32 weeks of gestation) are known to be at risk for neurocognitive handicaps in later life. The neurodevelopmental prognosis can be predicted by neonatal ultrasonography, but little is known about their function in later life. A cohort of 105 infants born before 33 weeks of gestation in 1979-1980 who had neonatal ultrasonograms were studied prospectively at 1, 4, and 8 years. At ages 14-15 years, 72 of these infants who remained in the United Kingdom (cases), and 21 age-matched controls who were born full term underwent brain MRIs as well as neurological, cognitive, and behavioral assessments. Of the 72 cases, 40 (55%) had unequivocally abnormal MRIs and an additional 15 had equivocally abnormal scans. Of the 21 controls, one (5%) had abnormal and five had equivocally abnormal MRI scans. Abnormalities of the ventricles, corpus callosum, and white matter were common in the cases. More brain lesions were identified by MRIs than had been noted by neonatal ultrasonography. The cases had significantly more reading, adjustment, and neurological impairments than controls, and their degree of behavioral impairment was significantly related to MRI abnormality.

### ■ COMMENT BY LAURA MENT, MD, FAAP

Preterm (PT) birth results in significant developmental disability, and several recent reports have suggested that cognitive outcome may be directly related to gestational age at birth. Neonates of less

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than 1250 g birth weight now represent almost 2% of all live births in the United States, and the survival rates of these infants approaches 85-90%. In conjunction with reports of increased survival, however, are troublesome data concerning long-term handicaps in these very low birth weight infants who often are critically ill in the first weeks and months of life.<sup>1</sup> Bhushan reported an increase in cerebral palsy, which he attributed to the increasing prevalence of PT birth,<sup>2</sup> and two studies have independently demonstrated that the incidence of cognitive deficits in this population has not changed over the past decade.<sup>3,4</sup> Depending on the birth weights of the patient cohort examined and the years in which they were born, the incidence of major neurodevelopmental handicaps in very preterm infants ranges from 12-32%.<sup>5,6</sup> In addition, it is these PT infants in whom high incidences of behavioral and school difficulties are now emerging. At age 8 years, more than half require special assistance in school, almost one-fifth are educated in designated special education classrooms, and 16% have repeated at least one grade.<sup>1,6</sup> Such data suggest that strategies for identifying causes of disability in this population of patients are essential.

The study of Stewart and her colleagues is an

extremely important one, therefore, because it begins for the first time to explore the structure-function relationship in the developing preterm brain. Stewart et al performed long-term follow-up studies of a group of very preterm infants who had neonatal cranial ultrasounds. Serial neurodevelopmental assessments were done on surviving study children, and MRI scans were performed on 72 children at age 14-15 years. These children were compared with 21 age-matched children born at term who served as controls. Both cases and controls were evaluated with cognitive, behavioral, and standard neurologic examinations.

MRI studies were considered to be normal in only 17 of the 72 (24%) preterm subjects; studies were equivocal in 15 (21%) and abnormal in 40 children (55%). For the term control children, studies were normal in 15 (71%), equivocal in five (24%), and abnormal in one (5%). The most common MRI abnormalities reported were ventricular dilatation, thinning or atrophy of the posterior body of the corpus callosum, and abnormal white matter signal; overall, 36 of the 72 (50%) preterm subjects had abnormalities of cortical white matter on MRI. In addition, although the specificity of neonatal cranial ultrasonography for predicting abnormal MRI at age 14-15 years was 94%, the sensitivity of this measure was only 22%. Those children who had neonatal ventriculomegaly were most likely to have abnormal MRI studies 14 years later.

For outcome assessment, preterm subjects were grouped into those with normal, equivocal, and abnormal MRI scans. Overall, preterm subjects were at much higher risk than term children for cognitive and neurologic abnormalities but Stewart et al were unable to detect significant differences in the incidences of cognitive, visual motor, or neurologic abnormalities between the preterm children with normal, equivocal, or abnormal MRI studies. Only the Rutter behavioral scores showed a clear association with abnormal cerebral MRI.

Stewart et al have made an important contribution to the understanding of the influence of preterm birth on cognitive outcome in adolescence. They have demonstrated what many investigators have long suspected but were unable to prove: children born prematurely are at high risk for structural CNS abnormalities. In this, the close of the NIH Decade of the Brain, these studies provide important baseline data. Future MRI studies will surely include diffusion-weighted imaging (DWI) analysis of axonal development and myelination 13 and 1H spectroscopic determinations of regional N-acetyl aspartate levels to approximate neuronal counts and synapse number. Finally, functional MRI (fMRI) studies may permit the exploration of the structure/function relation-

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#### Questions & Comments

Please call Robin Mason, Assistant Managing Editor, at (404) 262-5517 or Michelle Moran, Copy Editor, at (404) 262-5589 between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

ship in the developing brain.<sup>7</sup> (Dr. Ment is Professor of Pediatrics and Neurology at the Yale University School of Medicine.) ♦

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## Effect (or Noneffect) of Oral Androstenedione on Serum Testosterone and Muscle Performance

### A B S T R A C T & C O M M E N T A R Y

**Synopsis:** Androstenedione supplementation does not increase serum testosterone concentrations or enhance skeletal muscle adaptation to training.

**Source:** King DS, et al. Effect of oral androstenedione on serum testosterone and adaptations to resistance training in young men: A randomized controlled trial. *JAMA* 1999; 281:2020-2028.

Androstenedione, a precursor to testosterone, is normally produced by the adrenal glands

and testes and is converted to testosterone. Androstenedione is also produced by some plants and has been marketed as a product to increase blood testosterone levels and to be used as a “natural” alternative to anabolic steroid use. However, whether androstenedione actually increases blood testosterone or produces anabolic androgenic effects or has toxicity is not known. It is also known that androstenedione may be converted to estrogen directly. King and associates from the Exercise Biochemistry Laboratory at the University of Iowa conducted an eight-week randomized, controlled study of 20 healthy, normotestostrogenic men 19-29 years of age who performed eight weeks of whole-body resistance training. The subjects were randomized to receive either 300 mg/day of androstenedione or placebo. Levels of serum-free testosterone and total testosterone were not increased by androstenedione administration. Serum estrone increased significantly in the treatment group. No significant differences in skeletal muscle adaptation were seen between the two groups. However, there were no changes in the liver function tests of control or treatment groups. King et al conclude that eight weeks of androstenedione supplementation does not increase serum testosterone concentrations or enhance skeletal muscle adaptation to training.

### COMMENT BY MYRON GENEL, MD, FAAP

Pediatricians should welcome this study, since it provides some counterbalance to the “hoopla” that accompanied the use of androstenedione as a “nutritional supplement” to increase athletic performance. While promotional materials for androstenedione have been popular for some time within the fitness and muscle-building communities, much of the current hype stems from the disclosure by Mark McGwire during his record-setting home run output during the 1998 baseball season that he had been using androstenedione as a supplement to a rigorous strengthening program. Billed as a “natural” precursor of testosterone, androstenedione sales have boomed, especially among athletes who believe this is a safe alternative to anabolic steroids. The *JAMA* study, designed and performed by a group highly skilled in both medicine and athletics, demonstrates quite nicely not only that androstenedione administration does not increase serum testosterone levels but also that it is a precursor to naturally circulating estrogens. This may be particularly significant for male athletes during adolescence, when they are especially prone to develop gynecomastia. It has been common for me to see fairly accomplished adolescent male athletes who did not shower with their teammates because of embarrassment over presumably

natural gynecomastia. Since the *JAMA* study failed to detect any difference in muscular response to resistance training, albeit over a relatively short eight-week period, perhaps pediatricians can use this finding to dissuade adolescents from taking androstenedione as well as other putative enhancers of athletic performance. However, whether this advice will be accepted is dubious, for I am convinced that many dedicated athletes from junior high school on will consider doing or taking almost anything they believe may enhance their performance—even marginally. ♦

## Antibiotic Resistance in *E. coli* Urinary Tract Infections

### ABSTRACT & COMMENTARY

**Synopsis:** Risk factors for antimicrobial resistance among *E. coli* urinary tract infections (UTIs) were identified in a population of children seen at a tertiary care center in Ontario over a two-year period. Increasing resistance of *E. coli* to common, inexpensive, and well-tolerated antibiotics was noted and their use as prophylactic agents should be re-examined.

**Source:** Allen UD, et al. Risk factors for resistance to "first line" antimicrobials among urinary tract isolates of *Escherichia coli* in children. *Canadian Medical Association Journal* 1999;160:1436-1440.

Allen and colleagues studied 1636 consecutive *Escherichia coli* isolates from 967 children with urinary tract isolates (UTI) at a children's hospital in Canada over a two-year period (1992-1994). Their goal was to determine the prevalence of resistance to commonly used antibiotics for treatment of UTI and to identify risk factors associated with this resistance. Risk factors were identified using a case-control study in which 274 children with *E. coli* resistant to trimethoprim-sulfamethoxazole (Tmp-Smx) were matched with children with Tmp-Smx-sensitive isolates.

There was a disturbingly high prevalence of resistance among *E. coli* isolates to ampicillin (45%) and Tmp-Smx (31%) and to both ampicillin and Tmp-Smx (22%). As expected, resistance to nitrofurantoin (2%), gentamicin (3%), and cefotaxime (0.1%) was much less. Approximately 1.7% of the isolates were resistant to both ampicillin and gentamicin, which, as Allen et al point out, may begin to have implications in the choice of empiric antibiotic therapy for neonatal sepsis in their population.

Risk factors for antibiotic resistance included: 1) antibiotic treatment for more than four weeks in the preceding six months (OR\*14); 2) the presence of urinary tract abnormalities including vesicoureteral reflux (OR 4); 3) hospitalization within the past year (OR 2-4); 4) the presence of a malignant disease (OR 5); 5) antibiotic prophylaxis for immunodeficiency (OR 15); and 6) older age, since children younger than 2 years were three times less likely to be infected with resistant organisms. The incidence of pyelonephritis was not greater in the Tmp-Smx-resistant group.

Allen et al conclude that the role of commonly used, inexpensive antibiotics such as ampicillin and Tmp-Smx in the outpatient treatment and prevention of urinary tract infections requires re-examination, particularly in children who have recently received antibiotic therapy.

### ■ COMMENT BY THOMAS L. KENNEDY, MD, FAAP

We are all concerned about the growing problem of antimicrobial resistance spurred on by the extensive use, and sometimes overuse, of antibiotics. Knowing the magnitude of the problem for a given locale can be helpful in the choice of antibiotics. Additionally, however, identifying other risk factors can assist not only in the selection of antibiotics, but also in the development of strategies to avoid antibiotic use in certain populations if possible. For years, we have worried that the administration of "first-line" drugs such as amoxicillin for prophylaxis might lead to resistance as a result of antimicrobial pressure. The finding that four or more weeks of antibiotic use in the preceding six-month period is associated with resistance appears to support that concern. The other risk factors listed above are not surprising and make sense: things such as being in the hospital, having an immunodeficiency, or being younger and not having been treated with many courses of antibiotics. The absence of an association with pyelonephritis is somewhat surprising because, at least simplistically, one often equates more aggressive with more resistant organisms.

The findings in this study suggest that the use of nitrofurantoin, which has a low rate of resistance by *E. coli*, continues to be a good choice for urinary tract prophylaxis. It is, after all, safe, effective, and inexpensive. Unfortunately, it is not a favorite, either for parents or children, in terms of taste and acceptability, but you can't have everything. Other approaches, such as alternating antibiotics, may also demonstrate effectiveness and should be studied further. ♦

\*(OR = odds ratio, or the odds of having the risk factor if the condition [e.g., Tmp-Smx resistance] is present divided by the odds of having the risk factor if the condition is not present.)

# Injury in High School Basketball Players

ABSTRACT & COMMENTARY

**Synopsis:** *The rate of reportable injuries during a single high school basketball season was 0.56 for boys and 0.49 among girl athletes, and the risk of injury per hour of exposure was not significantly different between genders. However, female athletes had a significantly higher rate of knee injuries. For both sexes, the risk of injury during a game was significantly higher than during practice.*

**Source:** Messina DF, et al. The incidence of injury in Texas high school basketball: A prospective study among male and female athletes. *Am J Sports Med* 1999;27:294-299.

This is a prospective study of the incidence of injuries among high school basketball players in 100 Texas high schools during two seasons. Both male and female basketball players were analyzed. The athletic trainer at each high school reported injuries to the University Interscholastic League in Austin, Texas. A reportable injury was defined as one that occurred during a game or practice, that resulted in missed practice or game time, required a physician consultation, or involved the head or neck. The rate of injury was 0.56% for boys and 0.49% for girls. The risk of injury per hour was not statistically different between the two groups. In both gender groups, the most common injuries were sprains and the most injured area was the ankle, followed by the knee. Female athletes had a significantly higher rate of knee injuries, including a 3.79 greater risk of anterior cruciate ligament (ACL) injury. For both boys and girls the risk of injury was higher during game play than practice.

## ■ COMMENT BY BARRY GOLDBERG, MD, FAAP

This study by Messina and colleagues from the Orthopaedic Department at the University of Texas Health Service in San Antonio presents another example of the issues of gender differences in the frequency, site, and severity of sports-related injuries. Early studies indicated that women had an overall higher injury in sport-specific activities. This difference, if real, may have been related to skill and lack of conditioning. With time and better and more consistent study designs, it has been repeatedly demonstrated that injury rates are, in fact, now similar. This may be related to improved training, conditioning, and skill in girls.

As injury studies became more sport-specific, a rather constant finding has been the higher incidence of ACL injuries in women in basketball and soccer. The previously mentioned differences in conditioning and skill were raised as causes, but also implicated were intrinsic hormonal factors, gender differences in joint laxity, strength differences, as well as variations in bone morphology, such as the size of the intercondylar notch. Though there may be other specific causes that have yet to be determined, it is clear that there are sports-specific gender difference in injuries such as the increased frequency of stress fractures in female runners.

Despite the lack of definitive evidence of causative variables, the physician caring for athletes should be aware of the risks and introduce preventive measures wherever possible. In basketball this will require a careful preparticipation examination of the ankles and knees to ascertain strength and joint laxity and complete rehabilitation from prior injuries. It has been my experience that weakness and joint laxity predispose to significant ligamentous injuries in high-velocity contact sports. The findings of these characteristics should initiate the recommendation of a season-long strength program, as well as the use of external support in extreme circumstances. Of course, conditioning training and skill development should always be a component of the program, as should attention to proper nutrition and appropriate hormonal balance. (Dr. Goldberg is Head of the Sports Medicine Clinic at Yale University.) ♦

## Special Feature

### Updated Varicella Vaccine Recommendations

By Hal B. Jenson, MD, FAAP

The advisory committee on immunization practices (ACIP) of the Centers for Disease Control and Prevention (CDC) has issued updated varicella vaccine recommendations<sup>1</sup> of the original CDC recommendations published in 1996.<sup>2</sup> These expanded recommendations include: 1) establishing requirements for child day-care and school entry; 2) vaccination following exposure of susceptible persons to varicella, and for outbreak control; 3) expanded recommendations for vaccination of susceptible adolescents and adults at high risk for exposure or transmission; and 4) vaccination for persons with humoral immune deficiencies, and for some children infected with human immunodeficiency virus (HIV).

The ACIP also reviewed postlicensure adverse events reportedly associated with the varicella vaccine.

### **Updated Varicella Vaccine Recommendations**

**Daycare and School Entry Requirements.** Because the incidence of varicella is highest among children 1-6 years of age, vaccination during early childhood will have the greatest effect on reducing the incidence of disease. The ACIP now recommends that all states require that children entering child daycare facilities and elementary schools either have received varicella vaccine or have other evidence of immunity to varicella. Because school vaccine requirements are set at the state level, there will likely be some disparity across the United States in actual requirements. Already, 10 states have enacted requirements for varicella vaccination, and additional requirements are pending in many other states. Evidence of immunity includes either: 1) varicella vaccination; 2) a physician's diagnosis of varicella; 3) a "reliable history of the disease"; or 4) serologic evidence of immunity. The ACIP also suggests that "states should also consider implementing a policy that requires evidence of vaccination or other evidence of immunity for children entering middle school (or junior high school)."

**Postexposure Vaccination.** There are data from the United States and Japan following varicella exposure in household, hospital, and community settings that varicella vaccine is effective in preventing illness or modifying varicella severity if given within three days, and possibly up to five days, of exposure.<sup>3-5</sup> The ACIP now recommends that varicella vaccine be given to susceptible persons following exposure to varicella. If exposure does not result in disease, then vaccination will provide protection for subsequent exposure. There is no evidence that vaccination during the presymptomatic or prodromal stage of varicella increases the risk for complications or vaccine-associated adverse events, or that administration of live virus vaccines to persons with pre-existing immunity is associated with any adverse effects. The need for postexposure prophylaxis of healthcare workers should be minimal because all healthcare workers should be immune to varicella (as well as to measles and rubella).<sup>6</sup>

**Vaccination of Persons Younger than 13 Years of Age.** Varicella vaccine has been recommended since 1996 for susceptible persons younger than 13 years of age at high risk for exposure or transmission; the updated recommendations now include susceptible adolescents and adults living in households with children as a new high-risk group. The recommendations for varicella vaccination of susceptible persons younger than 13 years of age now includes: 1) persons who live or work in environments where transmission of VZV is likely, such as teachers of young children, child daycare employees, and residents and staff members in institutional settings; 2) persons who live and work in environments where transmission can occur, such as college students, inmates and staff members of correctional institutions, and military personnel; 3) nonpregnant women of childbearing age; 4) adolescents and adults living in households with children; and 5) international travelers.

**Persons with Altered Immunity** The previous ACIP recommendations stated that varicella vaccine not be administered to any person with primary or acquired immune deficiency. The ACIP maintains the recommendation against varicella immunization of persons with cellular immunodeficiencies, but now recommends that persons with impaired humoral immunity may be vaccinated. In addition, some HIV-infected children, who are at greater risk for complications of varicella and zoster

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compared to healthy children, may now be considered for varicella vaccination. Unpublished data from the Pediatric AIDS Clinical Trial Group indicate that two doses of varicella vaccine administered to HIV-infected children with asymptomatic or mildly asymptomatic disease are immunogenic and effective. HIV-infected children who are CDC class N1 ("no signs or symptoms") or A1 ("mild signs or symptoms") and have age-specific CD4+ T lymphocyte percentages  $\geq 25\%$  are eligible, and "varicella vaccine should be considered." The vaccination regimen for these children is two doses of varicella vaccine three months apart.

The vaccine has not been licensed for persons with blood dyscrasias, leukemia, lymphoma of any type, or other malignant neoplasms affecting the bone marrow or lymphatic systems. Varicella vaccine is available from the manufacturer (Merck) through a compassionate use protocol for children with acute lymphocytic leukemia (ALL) who are in remission, provided local approval by the appropriate institutional review board and informed consent have been obtained.

### **Update of Adverse Events Since Licensure**

From March 1995 to July 1998, a total of 9.7 million doses of varicella vaccine were distributed in the United States. The Vaccine Adverse Event Reporting System (VAERS) has received 6850 reports of adverse events, approximately two-thirds of which are in children younger than 4 years of age. The most frequently reported adverse event is rash, which occurs at a rate of 37 per 100,000 vaccine doses. However, PCR analysis showed that most postvaccination rash illnesses occurring within two weeks of vaccination were caused by wild-type varicella-zoster virus. For other serious adverse events that have been reported, the rates following vaccination are lower than the expected levels after natural varicella infection or than the background rates of disease in the community. This finding confirms that vaccination is safer than natural infection, even though chickenpox in children is thought of as a benign disease.

**Development of Zoster.** The VAERS rate of zoster after varicella vaccination was 2.6 per 100,000 vaccine doses, less than the overall rate of zoster of 215 per 100,000 person years, or the rate among healthy children after natural varicella infection of 68 per 100,000 person years. Cases of postvaccination herpes zoster have been confirmed by PCR to be due to both vaccine virus and wild-type virus, suggesting that some cases of zoster in vaccinees actually result from antecedent natural varicella infection.

**Transmission of Vaccine Virus.** Transmission of vaccine virus is rare, and has only been documented on

three occasions. All three cases resulted in mild disease without complications. In one case, a 12-month-old child transmitted the virus to his pregnant mother, who elected to terminate pregnancy. No vaccine virus was found in fetal tissue by PCR analysis. The other cases involved two 1-year-old children who transmitted vaccine virus to a healthy sibling and to a healthy father. Secondary transmission has not been documented in the absence of a postvaccination vesicular rash.

### **Conclusions**

The varicella vaccine has been used extensively with good efficacy and safety. The updated recommendations reflect the experience and results of ongoing investigations of postexposure prophylaxis and use in HIV-infected children. Immunization for varicella is an important component of the recommended childhood vaccine regimen and should be provided to all children beginning at 12 months of age, to susceptible older children to the 13th birthday, and to susceptible family members of households with children. In addition, varicella vaccine should be used for postexposure prophylaxis of susceptible persons.

It is important to ensure that all children for whom vaccination is recommended receive the vaccine. Increased varicella vaccination levels in the community will mean less circulating wild-type virus and less exposure during childhood, with a greater likelihood of disease during adulthood and the associated higher risk of serious complications, including death. ♦

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(ACIP) and the Hospital Infection Control Practices Advisory Committee (HICPAC). *MMWR Morb Mortal Wkly Rept* 1997;46(RR-18):1-42.

## CME Questions

- 7. True statements about long-term follow-up of surviving children who were born very preterm include all of the following except:**
- The reported incidence of major neurologic handicaps ranges from 12-20%.
  - More than half of these individuals require special assistance in school.
  - The frequency of abnormal MRIs can be accurately predicted by neonatal ultrasonography.
  - Half of these individuals have cortical white matter abnormalities on MRI.
- 8. Administration of oral androstenedione to healthy young men for eight weeks:**
- has a demonstrable positive effect on skeletal muscle adaptation to adaptation to a regimen of conditioning.
  - increases level of serum testosterone.
  - increases levels of serum estrogens.
  - is associated with abnormalities of liver function.
- 9. True statements about sports-related injuries include all of the following except:**
- They currently are significantly higher in girls than in boys.
  - In the past, gender differences in incidence may have been related to lack of skill and proper conditioning.
  - There is a higher rate of stress fractures in female than in male runners.
  - There is a higher frequency of knee injuries in female than in male athletes.
- 10. True statements from the latest ACIP recommendations for varicella immunization include all of the following except:**
- All susceptible children entering daycare or elementary school should be immunized.
  - Evidence for lack of susceptibility includes a reliable history or diagnosis of varicella, a previous immunization, or a positive serologic test.
  - All susceptible children with HIV infections should be immunized.
  - Immunization has a higher rate of complications than natural infection.
- 11. Risk factors for Tmp/Smx antibiotic resistance of cultured *E. coli* include all of the following except:**
- Age older than 6 years.
  - Antibiotic treatment for more than four weeks in the preceding six months.

- A history of pyelonephritis.
- Grade 4 vesico-ureteral reflux.

## Readers are Invited...

Readers are invited to submit questions or comments on material seen in or relevant to *Pediatric & Adolescent Medicine Reports*. Send your questions to: Michelle Moran—Reader Questions, *Pediatric & Adolescent Medicine Reports*, c/o American Health Consultants, P.O. Box 740059, Atlanta, GA 30374. Or, you can reach the editors and customer service personnel for *Pediatric & Adolescent Medicine Reports* via the Internet by sending e-mail to michelle.moran@medec.com. We look forward to hearing from you. ♦

## Hospital Manager's Y2K Crisis Manual

As the Y2K issue moves far beyond a mere "technological" issue, American Health Consultants has published the *Hospital Manager's Y2K Crisis Manual, a compilation of resources for nontechnical hospital managers*.

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## In Future Issues:

Bruising in Normal Infants