Questions and Answers

New Requirements.—Congress recently passed *The Copyright Revision Act of 1976* which affects JAMA's procedure for acceptance of submissions. Please refer to the "Instructions for Authors" page for details.

Routine Use of Anti-Rh γ-Globulin in Rh-Negative Newborns Not Recommended

Q An article in *Clinical Obstetrics and Gynecology* (17:95-114, 1974) has given rise locally to questions about the advisability of giving human Rh_o(D) immune globulin (Rhogam) to all Rh-negative newborn girls born of Rh-positive mothers. The article states:

There are a small number of Rh-negative women who have circulating Rh_o(D) antibody during their first pregnancy and who have not had abortions or incompatible blood transfusions. If the mothers of these women were Rh_o(D) positive, there is a possibility that the women are sensitized in the neonatal period by maternal cells transferred during labor and delivery. . . . An obvious way to prevent this neonatal sensitization would be to administer Rh_o(D) immune globulin very soon after birth to all Rh-negative females born to Rh-positive mothers.

Do you agree that anti-Rh γ-globulin should be routinely administered to all Rh-negative newborn girls?

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A Complete prevention of Rh hemolytic diseases will require the protection of Rh-negative families from *all* opportunities for sensitization by Rh-positive RBCs. There is a small number of cases in which anti-Rh develops in the mother during her first pregnancy, and postdelivery administration of anti-Rh γ-globulin is ineffective. The question is whether this antibody has resulted from sensitization during an early stage of this first pregnancy or whether the antibody was a response to some earlier stimulus.

We have recently completed our study of 107 Rh-negative newborn infants born of Rh-positive mothers and have demonstrated that maternal fetal hemorrhage is rare (approximately 2%) and that Rh antibody produced during the first six months in Rh-negative babies is similarly rare (approximately 1%). Routine administration of anti-Rh γ-globulin to Rh-negative newborns is not indicated.

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What Routine Tests for Monitoring Patients Receiving Prolonged Anticoagulant Therapy?

Q A utilization committee has questioned whether there is need in patients receiving prolonged anticoagulant therapy for hematocrit and hemoglobin determinations, urinalysis and stool tests for occult blood in addition to each prothrombin level determination. Prothrombin level determinations are done at two- to four-week intervals once a maintenance dosage is established, and sometimes the routine history is insufficient to alert one to possible bleeding episodes. Is such complete monitoring considered necessary?

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A Medical economy and good patient care are both involved in the answer to this practical question. Prothrombin times within therapeutic range and a history that rules out visible bleeding should suffice. Hematocrit or hemoglobin determinations, urinalysis and stool tests for occult blood are not necessary with each prothrombin determination and are probably instances of laboratory overutilization.

These tests should be done (1) before administration of anticoagulants is begun, (2) if the prothrombin times are dangerously high (more than three times normal), (3) at six-month intervals even if prothrombin times are within therapeutic range. In these instances, occult blood loss may often indicate or unmask an occult bleeding lesion in the gastrointestinal or urinary tracts that existed beforehand or occurred subsequently. This bleeding may be independent of the anticoagulants or may be caused by the anticoagulants even at therapeutic prothrombin ranges.

Gross bleeding in the presence of abnormally high or even desirable prothrombin time levels also warrants a search for an underlying lesion.

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Topical Nasal Anesthesia With Cocaine

Q In his audiotape on the use of cocaine topically as a nasal anesthetic, Johns (*Audio-Digest Otorhinolaryngology* [Audio-Digest Foundation, Los Angeles] 9:23, 1976) states that a survey of rhinologists indicated that of 2,240 respondents, 48% use more than 200 mg cocaine topically, and some use far more. Is this considered safe? Are dosages of 400 to 500 mg of cocaine crystals moistened with epinephrine (Adrenalin), 1:1,000, considered safe, and is this amount widely used? Are either of these methods acceptable when combined with general anesthesia? Is there a reference that deals specifically with comparative absorptions of cocaine from the mucosa of different parts of the respiratory tract?

MD, Virginia

A The respondents to Johns' survey, who used more than 200 mg of cocaine topically, were using too much, according to Goodman and Gilman,[1] who state that no more than 200 mg should be used topically (4 ml of a 5% solution). From a practical point of view, I cannot conceive of the need to use more than this amount intranasally, and it is certainly not considered safe or necessary to exceed this dosage in the usual nasal plastic procedures.

The maximum safe dose of cocaine in a 70-kg human is stated to be in the range of 80 to 200 mg. The fatal dose of cocaine in man is stated to be 1.2 g, but severe toxic reactions have been reported with doses as low as 20 mg.

The use of crystals moistened with epinephrine is still in current use by some otolaryngologists, but they are in a definite minority. The theoretical advantages do not justify the increased risk of toxic reactions from the predictably higher serum levels.

Combining general anesthesia with the use of cocaine is acceptable as long as the cocaine is used with prudence and the anesthetist is aware of its use.

I know of no reference that deals specifically with comparative absorptions of cocaine from the mucosa of different parts of the respiratory tract. Though the modes of application are different in clinical practice, I would expect their absorption to be similar. Miller et al[2] have studied serum cocaine levels resulting from cocaine-treated pledgets placed in contact with the nasal mucosa.

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1. Goodman LS, Gilman A: The Pharmacological Basis of Therapeutics, ed 5. New York, Macmillan, 1975, p 388.
2. Miller SH, Dvorchik B, Davis TS: Cocaine concentrations in the blood during rhinoplasty. *Plast Reconstr Surg* 60:566-571, 1977.

A Maximum therapeutic doses for any drug are difficult to recommend. Accordingly, the oft-quoted dose limits for cocaine of 200 mg or 3 mg/kg are at best compromises between optimal efficacy and minimal toxicity. If, as stated in your inquiry, more than 1,000 physicians use more than 200 mg of cocaine topically, it would seem that the present upper limit is too low. However, you fail to mention side effects, so one cannot judge where the trade-off point lies.

Though no dose of any local anesthetic ever is "safe," 500 mg of cocaine is more than I would use topically. However, cocaine is usually applied nasally with swabs soaked in solution. Thus, only part of the drug reaches the nasal mucosa; the rest is discarded when the swab is removed.

Since cocaine is a potent vasoconstrictor in its own right, there is no evident need to add epinephrine to the crystals; this is an old practice that seems to die all too slowly. The cocaine-epinephrine mixture is particularly hazardous in the presence of general anesthesia when it could give rise to disturbing cardiac arrhythmias.

Van Dyke et al[1] have excellent blood level data in their recent paper, where other references to the literature may be found. Premedication with oral or intravenous diazepam (Valium) reduces the likelihood of toxic central reactions to local anesthetics[2] and thus may be advisable when recommended dose limits are approached. A recent paper confirms that 1.5 mg/kg of cocaine topically applied does not appear to exert any clinically significant sympathetic effect during general anesthesia.[3]

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1. Van Dyke C, Barash PG, Jatlow E, et al: Cocaine: Plasma concentrations after intranasal application in man. *Science* 191:859-861, 1976.
2. de Jong RH, Heavner JE: Diazepam prevents local anesthetic seizures. *Anesthesiology* 34:523-531, 1971.
3. Barash PG, Kopriva CJ, Stahl A, et al: Is cocaine a sympathetic stimulant under general anesthesia? Read before the annual meeting of the American Society of Anesthesiologists, New Orleans, October 15-19, 1977.

No Need To Abstain From Alcoholic Beverages After Recovery From Infectious Mononucleosis

Q A 16-year-old girl has made a full recovery from infectious mononucleosis accompanied by hepatitis. Her liver is no longer palpable, and results of all liver function tests have returned to normal. One physician warned her that she must always abstain from alcoholic beverages, while another advised her that she can lead a completely normal life, with no special precautions. Which one is right?

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A In general, infectious mononucleosis is a relatively benign disease with few complications and sequelae and with rare fatalities. From the standpoint of the liver, although deaths from liver necrosis have been reported, only two fatalities involving the liver have met critical analysis.[1]

From the available data, a patient who has infectious mononucleosis with liver involvement that has reflected abnormal results of liver function tests need observe no precautions whatsoever once results of the liver function tests have returned to normal. Accordingly, there appears to be no need for the girl to abstain from alcohol nor any reason not to lead a completely normal life.

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1. Penman HG: Fatal infectious mononucleosis: A critical review. *J Clin Pathol* 23:765-771, 1970.

What Is the Teratogenic Potential of Hydroxyprogesterone?

Q A woman was treated in early pregnancy with hydroxyprogesterone caproate (Delalutin). Is it possible that there may be some delayed effect of the treatment on her son who is now 7 years of age?

MD, Texas

A Two decades ago synthetic estrogens and progestins were frequently prescribed for the prevention of miscarriage. Subsequently, it became evident that such therapy was ineffective and was associated with the risk of serious side effects. The use of estrogens and progestins (but not progesterone) is now contraindicated in early pregnancy.

The side effects reported vary depending on the type of preparation used. Diethylstilbestrol, probably the most widely prescribed synthetic estrogen hormone for this indication, is associated with the development of vaginal adenosis in a majority of teen-age daughters of mothers thus treated in early pregnancy; vaginal adenocarcinoma occurs rarely. Sons of mothers thus treated have a higher than normal incidence of minor urogenital tract abnormalities. Data on the potential teratogenic effect of progestins is less specific due to the wider variety of compounds available and the fact that these agents were often used in combination with an estrogen. Progestins might have been administered in pregnancy for the prevention of miscarriage or as a hormonal pregnancy test; more recently, oral contraceptives might have been taken inadvertently during early pregnancy. Side effects reported to be associated with these uses include masculinization of female fetuses, limb reduction defects, and cardiovascular anomalies.

Your question concerns the possible delayed effects of treatment in early pregnancy with hydroxyprogesterone caproate on a 7-year-old male offspring. There is probably little cause for concern. This agent has been widely used during pregnancy, yet in a recent report on cardiovascular birth defects associated with hormonal treatment in pregnancy,[1] only one of 19 cases was associated with hydroxyprogesterone caproate use. Furthermore, if an anomaly existed, it would probably have been detected early in life.

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1. Heinonen OP, Slone D, Monson RR: Cardiovascular birth defects and antenatal exposure to female sex hormones. *N Engl J Med* 296:67-70, 1977.