

Pentamidine and Hypoglycemia

TO THE EDITOR: The recent case of pentamidine-induced hypoglycemia reported by Sharpe (1) prompted a chart review of patients treated with pentamidine at the Toronto General Hospital during the period of 1973 to 1983. Six of fifteen adult patients developed hypoglycemia (fasting plasma glucose less than 3.3 mmol/L) while being treated with pentamidine for *Pneumocystis carinii* pneumonia.

In comparison, the Parasitic Disease Drug Service, Centers for Disease Control (CDC), reported hypoglycemia in 25 (6.2%) of 404 patients treated with pentamidine (2). An earlier paper from the CDC reported hypoglycemia (blood glucose below 3.3 mmol/L) in 15 (9%) of 168 patients; however, only 2 patients developed symptoms of hypoglycemia (3). Hughes and associates (4) found 6 of 15 children who received pentamidine had blood glucose concentrations less than 3.3 mmol/L but only 1 child had hypoglycemic symptoms. Daily monitoring of blood sugar and prompt treatment when concentrations were less than 3.3 mmol/L may account for the low incidence of symptomatic hypoglycemia.

Recently, Bouchard and associates (5) reported in detail four cases of severe fasting hypoglycemia during pentamidine administration. These patients subsequently developed diabetes mellitus. Insulin therapy was required in three patients who survived for more than a few weeks.

Preliminary in-vitro studies suggest that pentamidine's paradoxical effects on blood glucose may arise from an early cytolytic release of insulin resulting in transient hypoglycemia (5), followed by diabetes mellitus due to beta-cell destruction and insulin deficiency. Clinical evidence supports this hypothesis. Hypoglycemia usually appears from 5 to 14 days after starting pentamidine but may occur after the first dose (5). The fall in blood sugar and hypoglycemic symptoms usually appear 1 to 2 hours after pentamidine administration and are accompanied by inappropriately high amounts of circulating insulin (5). Diabetes mellitus follows the hypoglycemic episodes by as few as 6 days but its appearance is more often delayed by several weeks (5). Administration of pentamidine to patients with diabetes mellitus, whether or not pentamidine-induced, does not result in further hypoglycemic attacks nor aggravation of diabetes (5).

The experience at Toronto General Hospital is similar to that reported in the literature and suggests that pentamidine-induced hypoglycemia is not an uncommon event. Furthermore, diabetes mellitus may occur in a few patients several weeks after treatment with pentamidine is completed. We share Dr. Sharpe's concern that clinicians should be aware of the effects of pentamidine on blood glucose. Monitoring of blood glucose before, during, and for several days after each course of pentamidine administration would be prudent.

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TO THE EDITOR: As noted by Dr. Sharpe (1), pentamidine-induced hypoglycemia is likely to become a common complica-

tion of the treatment of *Pneumocystis carinii* pneumonia associated with the acquired immunodeficiency syndrome. We first saw hypoglycemia in a patient treated for *P. carinii* pneumonia who also had chemotherapy for a diffuse histiocytic lymphoma. Subsequently we saw the same complication in a patient treated for *P. carinii* who also had the acquired immunodeficiency syndrome. Both of these patients (2) and several others with similar findings were successfully treated with diazoxide, 100 mg orally every 6 hours. During our study of the original two patients we determined that the hypoglycemia was associated with inappropriately elevated serum insulin levels (2). This finding has also been reported by Bouchard and colleagues (3) who successfully treated one patient with oral diazoxide. Although hypoglycemia occurs in from 5% (3) to 9% (4) of patients, the true incidence may well be higher when looked for carefully (3). For this complication, oral diazoxide is safe and effective treatment and can generally be discontinued approximately 10 days after pentamidine therapy is stopped.

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Bacterial Interference and Toxic Shock Syndrome

TO THE EDITOR: Although an etiologic association between toxic shock syndrome and vaginal colonization with *Staphylococcus aureus* is generally accepted as being beyond doubt, many questions regarding the pathogenesis of the syndrome remain unanswered. The ability of potentially pathogenic bacteria to colonize body surfaces may be enhanced by their production of inhibitory substances that restrict the growth of other bacteria (1). Evaluation of bacteriocin production by strains of *S. aureus* associated with toxic shock syndrome has been our primary interest. These proteinaceous antibiotic agents have inhibitory activity directed predominantly against other bacteria of either the same or closely-related species (2). In previous studies, *S. aureus* bacteriocins have been found most commonly in phage group II strains, particularly strains lysed by phage 71 alone (2, 3).

We examined 23 vaginal isolates of *S. aureus* associated with toxic shock syndrome and 27 isolates not associated with the syndrome (provided by P. Schlievert) for inhibitory activity against each other using a deferred antagonism method on blood agar medium (4). Although no significant bacteriocin-like inhibitory activity between the *S. aureus* strains could be found, all of these strains were strongly inhibitory for group N streptococcus strain T-21 (4) when this was used as an indicator. Aerobic incubation of the producer strains and the presence of human blood and calcium in the test medium were requirements for the demonstration of this inhibitory activity. The inhibitory substance was found to be dialyzable (6000 to 8000 molecular weight cut-off tubing) and was inactivated by heating at 60 °C for 30 minutes.

Using *Micrococcus radiodurans* strain CCM 2564 as an indicator, a second inhibitory substance was found that was preferentially produced by nonassociated *S. aureus* strains (23 out of 27) rather than associated strains (9 out of 23). This inhibitor was stable to heating at 60 °C for 30 minutes and was non-dialyzable (12 000 molecular weight cut-off tubing). Neither human blood nor Ca²⁺ enhanced production.

With the use of either *Streptococcus lactis* strain C2 or *S. diacetylactis* strain 18-16 (both obtained from L. McKay) as indicators, yet another inhibitor was found. This inhibitor was more commonly produced by strains associated with toxic shock syndrome (21 of 23 were positive) than nonassociated isolates (5 of 27). Properties of this associated inhibitor included inactivation on heating at 60°C for 30 minutes, and non-dialyzability (12 000 molecular weight cut-off tubing). Oxygen appeared to be required both for production and demonstration of the inhibitor. Inhibitory activity was enhanced by the presence of human blood and Ca²⁺. Previous studies have shown that an antigen (toxin) for toxic shock syndrome is produced predominantly by strains of *S. aureus* associated with the syndrome (5). We have found that production of this toxin and the inhibitor associated with the syndrome can occur independently in some *S. aureus* isolates. Moreover, toxic shock syndrome toxin preparations (provided by P. Schlievert) were without inhibitory activity against any of the indicator strains used in the present study.

The relationship of these inhibitory substances to other documented staphylococcal products has yet to be determined as has the range of their inhibitory activity against other bacterial species. Nevertheless, the production by vaginal *S. aureus* strains of various bacteriocin-like inhibitors, some apparently blood-dependent and one more frequently associated with toxic shock syndrome isolates, suggests a possible role for bacterial interference in the development of menstrual toxic shock syndrome. Detection of production of the associated inhibitor may provide another marker of *S. aureus* strains with the potential for inducing toxic shock syndrome.

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Diagnosis of Thromboembolic Pulmonary Hypertension

TO THE EDITOR: Moser and associates (1) have drawn appropriate attention to difficulties in establishing the diagnosis of chronic thromboembolic pulmonary hypertension. Symptoms or signs of thromboembolic disease may be absent or unrecognized, and recurrent emboli may simulate pneumonia with pleuritis, chronic bronchitis, and coronary, valvular, or congenital heart disease (2). Differentiation from primary pulmonary hypertension is frequently difficult. Noninvasive evaluations often lack specificity for thromboembolic disease, and direct demonstration of pulmonary arterial thrombi has previously been achieved only by angiography.

At the University of California, San Francisco, we have used rapid sequential computed tomographic scanning during the administration of 1.5 mL/kg of contrast (Conray 400; Mallinckrodt Inc., St. Louis, Missouri) by peripheral vein in evaluating

cases of thromboembolic pulmonary hypertension (3). Contiguous 1-cm scans were obtained through the chest at a rate of one scan every 3.4 s. We have found contrast-enhanced computed tomography particularly useful for delineating the proximal extent of thrombus, thus showing the feasibility of surgical thromboembolectomy as done by Moser and associates (1). The cross-sectional format of computed tomography eliminates many of the difficulties in angiographic interpretation noted by Moser and associates. Assessment of tissue density by tomography can differentiate thrombus from vessel wall (4) and the ability to reformat images in para-axial planes through vessels of interest allows visualization of thrombus structure and extent in any tomographic plane. Computed tomography has been well tolerated in these patients with severe pulmonary hypertension, and it is valuable in establishing the diagnosis as well as in follow-up of medical or surgical treatment in these patients. This information can be obtained with standard, commercially available tomographic body scanners and may prove helpful in establishing the ever elusive diagnosis of chronic thromboembolic pulmonary hypertension.

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Myocardial Ischemia and Ambulatory Monitoring

TO THE EDITOR: In their editorial (1) in the February 1983 issue, Armstrong and Morris cite several studies to support their conclusion that ambulatory electrocardiographic monitoring cannot confidently be used to diagnose coronary ischemia (1). Although this conclusion may be correct, the evidence cited is limited and inadequate.

The authors acknowledge early studies that showed a high frequency of ischemic ST segment depression in patients with proven coronary artery disease. They cite the study by Stern and colleagues (2) of 50 patients referred for severe chest pain. Twenty-two of these patients had abnormal resting electrocardiograms, and 16 developed abnormal ST segment responses during ambulatory recording. Fifteen of these 16 patients had greater than 60% obstruction of one or more coronary arteries. Sixteen of the 28 patients with normal resting electrocardiograms had positive ST changes on 24-hour ambulatory monitoring, and 13 of these had greater than 60% narrowing of one or more coronary arteries. An arteriogram showing more than 60% obstruction of one or more vessels was only found in 2 of the 12 patients with negative 24-hour recordings.

The authors cite their study of "healthy" Indiana state policemen with a mean age of 44.6 years (3). Thirty percent of these persons had abnormal S-T segment depression during the monitoring period, but none had coronary arteriographic examination. Further examples of "normal" subjects having abnormal ST responses on ambulatory monitoring are given. The study by Levy and Abinader (4) of patients during gastroscopic examination shows a 23.6% incidence of ST-T changes. These patients were screened for coronary disease with "a short cardiac history." The patients had a mean age of 62 years, and none had stress testing or arteriographic examination. The study by Taggart and associates (5) of ST depression in response to the