EXPERIENCE AND REASON—Briefly Recorded

"In Medicine one must pay attention not to plausible theorizing but to experience and reason together. . . . I agree that theorizing is to be approved, provided that it is based on facts, and systematically makes its deductions from what is observed. . . . But conclusions drawn from unaided reason can hardly be serviceable; only those drawn from observed fact." Hippocrates: *Precepts. (Short communications of factual material are published here. Comments and criticisms appear as Letters to the Editor.)*

Escherichia coli Sepsis and Prolonged Hypophosphatemia Following Exertional Heat Stroke

Because of the increasing emphasis on physical activity, sports medicine represents a growing proportion of medical care. Climatic heat stress, including heat stroke, is of sufficient concern that its preventability has been addressed by the American Academy of Pediatrics.[1] Although heat stroke is defined by the triad of hyperpyrexia, anhydrosis, and altered mental status, the clinical course of these patients may include multiple complications.[2-8] In this article we describe a previously unrecognized etiologic relationship between two of these complications, which may permit early identification and prevention of life-threatening consequences to heat stroke.

Two cases of Gram-negative sepsis have been described in previously healthy young adults suffering from fatal exertional heat stroke.[7,8] Hypophosphatemia may occur with heat stroke,[2,3,6,9,10] and, although hypophosphatemia and septicemia have not been linked previously in this condition, it is known that a low serum phosphate concentration may have a profound effect on the immune system and may be associated with Gram-negative sepsis.[11-17] We describe a 16-year-old boy who suffered exertional heat stroke while jogging in whom prolonged normocalcemic hypophosphatemia and Gram-negative septicemia subsequently developed. We propose that the hypophosphatemic state predisposed the patient to septicemia and suggest that aggressive treatment of his hypophosphatemia might have assisted in this recovery.

A 16-year-old boy was admitted to the Texas Children's Hospital (Houston) with complaints of generalized malaise and gross hematuria. The patient had been discharged from another hospital 36 hours previously after being treated for heat stroke. After jogging 9.7 km (6 mi) in an ambient temperature of 37.8°C (100°F), the boy collapsed.

During the initial hospitalization, the boy appeared unresponsive but well-developed and well-nourished. Rectal temperature was 41.1°C (106°F), pulse rate 150 beats per minute, respiratory rate 36 breaths per minute, and blood pressure 71/39 mm Hg.

Initial laboratory values while the boy received 40% oxygen included the following: arterial pH 7.32, P_{CO_2} 39 mm Hg, and P_{O_2} 166 mm Hg. Hemoglobin was 14.1 g/dL, hematocrit 43%, white blood cell count 5100/μL, and platelet count 177 000/μL. The serum sodium was 152 mEq/L, potassium 6.7 mEq/L, chloride 118 mEq/L and bicarbonate 16 mEq/L. Additional laboratory values included blood urea nitrogen 20 mg/dL, serum creatinine 2.6 mg/dL, serum calcium 8.8 mg/dL, serum phosphate 0.7 mg/dL, serum uric acid 5.1 mg/dL, total bilirubin 0.8 mg/dL, serum alkaline phosphatase 72 U/L (normal 50 to 136), alanine transaminase 8 U/L (normal 3 to 36), and aspartate transaminase 20 U/L (normal 5 to 40).

The patient was rehydrated intravenously and regained consciousness within 6 hours. After Foley catheter placement, results of urinalysis showed a specific gravity of 1.020 with a red cloudy color, pH 5, 3+ protein, small ketones, red blood cells that were too numerous to count, and no white blood cells. According to results of a repeat urinalysis after intravenous hydration, there was a specific gravity of <1.005 with yellow, hazy color, pH 5, 1+ blood, 0 red blood cells, 4 to 10 white blood cells, 4+ bacteria, and 11 to 21 phosphate crystals per

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high power field. The serum electrolytes returned to normal. Repeat serum calcium was 8.8 mg/dL, phosphate 2.4 mg/dL, uric acid 9.4 mg/dL, amylase 81 U/L, and creatine kinase 4941 U/L. The blood urea nitrogen and creatinine values were 23 mg/dL, and 1.5 mg/dL, respectively. The patient was discharged on the third hospital day.

At the time of admission to Texas Children's Hospital, the boy showed the following values: temperature 37.9°C, pulse rate 104 beats per minute, respiratory rate 28 breaths per minute, and blood pressure 120/68 mm Hg. His weight was 54.4 kg and his height was 169 cm. He had mild scleral icterus, liver span of 9.5 cm by percussion, and a palpable spleen tip.

Serum electrolytes, blood urea nitrogen, and serum creatinine values were normal. The hemoglobin was 13.8 g/dL, hematocrit 38%, platelets 74,000/μL and white blood cell count 7000/μL with a differential of 72% polymorphonuclear leukocytes, 16% bands, 11% lymphocytes, 1% monocytes. According to results of urinalysis, there was a specific gravity of 1.012, pH 6, 3+ protein, 3+ glucose, 231 to 275 white blood cells, and 3+ bacteria per high power field, no red blood cells, positive hemoglobin, phosphate crystals, and no detectable myoglobin. Serum calcium was 8.8 mg/dL, phosphate 0.6 mg/dL, and magnesium 2.1 mg/dL. Liver function tests included the following values: a serum glutamic oxaloacetic transaminase 2760 U/L, serum glutamic pyruvic transaminase 299 U/L, alkaline phosphatase 97 U/L, total bilirubin 2.1 mg/dL, direct bilirubin 0.4 mg/dL, and creatine kinase 297 U/L. The prothrombin time, partial thromboplastin time, amylase, renal ultrasound, electroencephalogram, and electrocardiogram results were all normal. Toxicology and hepatitis screens were negative.

The patient was started on oral phosphate supplementation (Neutraphos 1000 mg each day) and oral ampicillin pending urine culture results. The maximum temperature was 38.6°C and two sets of blood cultures were obtained within 24 hours.

On the third hospital day, the phosphate supplementation was increased to 2000 mg of oral phosphate supplementation each day. The platelet count continued to decrease, reaching a nadir of 44 000. The urine culture grew $>10^5$ *Escherichia coli* colonies per milliliter and both blood cultures grew *E coli*. All organisms were resistant to ampicillin. Ampicillin was discontinued and intravenous therapy with amikacin was initiated. On the fifth hospital day, the serum phosphate concentration was 2.4 mg/dL. On hospital day 8, with a serum phosphate concentration of 4.9 mg/dL, oral phosphate supplementation was discontinued. Serum phosphate and calcium concentrations remained normal and the platelet count, urinalysis, liver function tests, and liver span all returned to normal. Repeated blood and urine cultures were negative. The patient was discharged on the 13th hospital day.

DISCUSSION

Graber et al[8] described an 18-year-old man who suffered from fatal heat stroke following football practice. Urine cultures were negative for pathogens; however, blood cultures before and after death grew multiple Gram-negative rods. Assia et al[7] described fatal heat stroke in an 18-year-old male military recruit in whom bacteremia with Gram-negative rods and streptococci developed following a march. Stool, urine and cerebrospinal fluid specimens were sterile. Unfortunately, serum phosphate concentrations were not reported in either case.

Hypophosphatemia may be characterized by major systemic clinical signs and symptoms including anorexia, malaise, muscle weakness, seizures, rhabdomyolysis, hemolysis, thrombocytopenia and leukocyte dysfunction with impaired chemotaxis, phagocytosis, and intracellular killing.[11–15] Low serum phosphate concentrations have been associated with Gram-negative sepsis.[15–17] It has not been established whether the aberration in serum phosphate concentration predisposes the patient to or is a response to infection.[15] In an experimental model, low serum phosphate concentration may be seen as an effect of the infectious process.[18] We suggest that the course of our patient is consistent with the hypothesis that the hypophosphatemia caused an immune-compromised state and that Foley catheter insertion may have led to a bacterial cystitis and secondary dissemination into the blood stream. It is unlikely that our patient suffered from an asymptomatic ampicillin-resistant *E coli* urinary tract infection prior to the initial hospitalization. Thus hypophosphatemia as a result of prior infection is improbable in this case.

Our patient had a relatively mild febrile response considering the severity of the infectious process. Moreover, no fever occurred until after oral phosphate supplementation was started. The inability to mount an appropriate febrile response may have been due to dysfunctional white blood cells. The patient also suffered from thrombocytopenia, which may occur in patients with hypophosphatemia or Gram-negative septicemia.[9,14–16] Patients have been described who had hypophosphatemia induced by hyperpyrexia and also had thrombocytopenia.[4,6,9,10]

Hypophosphatemia induced by heat stroke has been described previously, but usually has been associated with abnormal serum calcium concentrations.[6,9,10] Explanations for this phenomenon have included respiratory alkalosis associated with increased cellular uptake of serum phosphate.[9,10]

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However, several patients, including the boy described in this article, suffered from hypophosphatemia and heat stroke without evidence of this type of acid base disturbance.[2,4] In several reports, hypophosphatemia has been attributed to rhabdomyolysis with calcium phosphate precipitation into soft tissues.[6,19] The normal serum calcium concentrations in this patient are not consistent with this proposed model. It would have been helpful to calculate the urinary excretion of phosphate during the boy's first hospitalization to determine whether urinary phosphate losses were responsible for the observed hypophosphatemia.

Septicemia is a life-threatening complication of heat stroke. Although we can not prove conclusively that hypophosphatemia is the causative factor in Gram-negative septicemia associated with heat stroke, the course of the patient we describe is consistent with this hypothesis. Physicians should measure serum phosphate in patients with heat stroke and treat hypophosphatemia aggressively. It is also important to consider obtaining appropriate cultures and initiating antimicrobial therapy in patients suffering from heat stroke.

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REFERENCES

1. American Academy of Pediatrics, Committee on Sports Medicine. Climatic heat stress and the exercising child. *Pediatrics.* 1982;69:808–809
2. Spring CL, Portocarrero CJ, Fernaine AV, et al. The metabolic and respiratory alterations of heat stroke. *Arch Intern Med.* 1980;140:665–669
3. Graham BS, Lichtenstein MJ, Hinson JM, Theil GB. Nonexertional heatstroke: physiologic management and cooling in 14 patients. *Arch Intern Med.* 1986;146:87–90
4. Hart GR, Anderson RJ, Crumpler CP, et al. Epidemic classical heat stroke: clinical characteristics and course of 28 patients. *Medicine* 1982;61:189–197
5. Fidler S, Fagan E, Williams R, et al. Heatstroke and rhabdomyolysis presenting as fulminant hepatic failure. *Postgrad Med J.* 1988;64:157–159
6. Mason J, Thomas E. Rhabdomyolysis from heat hyperpyrexia: Severe hypocalcemia and hypophosphatemia as complicating factors. *JAMA.* 1976;235:633–634
7. Assia E, Epstein Y, Shapiro Y. Fatal heatstroke after a short march at night: A case report. *Aviat Space Environ Med.* 1985;56:441–442
8. Graber CD, Reinhold RB, Breman JG, et al. Fatal heat stroke—circulating endotoxin and gram-negative sepsis as complications. *JAMA.* 1971;216:1195–1196
9. Knochel JP, Caskey JH. The mechanism of hypophosphatemia in acute heat stroke. *JAMA.* 1977;238:425–426
10. Hanson PG, Zimmerman SW. Exertional heat stroke in novice runners. *JAMA.* 1979;242:154–157
11. Stoff JS. Phosphate homeostasis and hypophosphatemia. *Am J Med.* 1982;72:489–495
12. Lloyd CW, Johnson CE. Management of hypophosphatemia. *Therapy Rev.* 1988;7:123–128
13. Craddock PR, Yawata Y, Van Santen L, et al. Acquired phagocyte dysfunction. *N Engl J Med.* 1974;290:1403–1407
14. Knochel JP. The pathophysiology and clinical characteristics of severe hypophosphatemia. *Arch Intern Med.* 1977;137:203–219
15. Fitzgerald FT. Hypophosphatemia. *Adv Intern Med.* 1978;32:137–157
16. Shöenfeld Y, Hager S, Berliner S, et al. Hypophosphatemia as diagnostic aid in sepsis. *NY State J Med.* 1982;82:163–165
17. Riedler GF, Scheitlin WA. Hypophosphatemia in septicemia: Higher incidence in gram-negative than in gram-positive infections. *Br Med J.* 1969;1:753–756
18. Gainer GB, Heubner PE, O'Dell BL. Dietary phosphorus and salmonellosis in guinea pigs. *Fed Proc.* 1967;26:799
19. Grossman RA, Hamilton RW, Morse BM, et al. Nontraumatic rhabdomyolysis and acute renal failure. *N Engl J Med.* 1974;291:807–811

Growth Hormone Deficiency in an 8-Year-Old Girl With Human Immunodeficiency Virus Infection

Abnormalities of hypothalamic pituitary function have been reported in adult subjects with human immunodeficiency virus (HIV) infection.[1–3] However, endocrine studies in children with HIV infection have failed to disclose significant hormonal abnormalities.[4] Indeed, children infected with HIV who were growing poorly were found to have opportunistic infections and lower levels of T-helper cells, but normal growth hormone or insulin-like growth factor 1 concentrations.[4]

Herein we describe an 8-year-old girl with perinatally acquired HIV infection, growth deceleration, and isolated growth hormone deficiency.

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CASE REPORT

This 8 ½-year-old female child was referred to the pediatric endocrine clinic for evaluation of growth deceleration. From 2 to 7 years of age, she grew at a rate of 5.1 cm/y, and remained in above the 5th percentile for height (Fig 1). From 7 to 8 ½ years of age, her height velocity fell to 2.5 cm/y; and at the time of her referral

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