Impact of Mild Chronic Hyponatremia on Falls, Fractures, Osteoporosis, and Death

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Abstract

There is emerging evidence that mild chronic hyponatremia (MCH), highly prevalent in the elderly and once considered asymptomatic, is a major independent risk factor for falls, fall-related fractures (independent of osteoporosis, age, and sex), impaired attention and gait, reductions in bone mineral density (BMD), and even death.

Although research on MCH and bone health is emerging and ongoing, it has not been recognized in orthopedics. Orthopedic surgeons must be educated regarding the impact of hyponatremia on bone, as osteoporotic fractures have enormous socioeconomic consequences, and the problem will worsen. Orthopedic surgeons should also be included in research, in education, and in the establishment of diagnostic and treatment protocols.

In this article, we review the current concepts of MCH and its impacts on the skeletal system.

Hyponatremia (serum sodium, <135 mmol/L) is the most common electrolyte disorder in humans, affecting 1% to 4% of the total population.[1,2] Incidence is highest among the elderly, affecting 7% to 53%.[1,3] Acute or severe hyponatremia causes various signs and symptoms: muscle cramps, nausea, vomiting, headache, weakness, fatigue, lethargy, confusion, disorientation, seizure, coma, cardiorespiratory arrest, brain stem herniation, and death.[4,5] Bone fractures have also been reported as an initial manifestation of hyponatremic encephalopathy.[6,7] In contrast, mild chronic hyponatremia (MCH) does not have easily recognizable signs and symptoms, and thus has been traditionally considered asymptomatic and not in need of treatment.[5] However, emerging evidence demonstrates that MCH is a serious condition with significant consequences.[8-19] Over the past decade, MCH has been found to create subtle impairments in gait and attention (leading to falls), decrease bone mineral density (BMD), and exacerbate osteoporosis; it has even been associated with increased mortality.[8-19]

Although the impact of hyponatremia on bone health is gaining interest among other specialties, the concept is not emphasized in orthopedics. Orthopedic surgeons must be educated regarding the topic, as osteoporotic fractures have enormous socioeconomic consequences, and the problem will worsen. Orthopedic surgeons should also be included in research, education, and the establishment of protocols for diagnosis and treatment. This article reviews the current concepts of MCH and its impact on the skeletal system.

Socioeconomic Impact of Osteoporotic Fractures

The annual incidence of falls in the elderly is high, and their socioeconomic burdens are heavy. Approximately 30% of people between ages 65 and 80, and 50% of people older than 80, fall at least once each year.[20] Approximately 1% of these falls cause a hip fracture,[21] and 4% to 6% cause other fractures.[11] In 1990, osteoporotic hip fractures led to 300,000 hospitalizations in the United States[22] and 1.7 million worldwide.[18] By 2040, these numbers are expected to reach 512,000 and 6.3 million, respectively.[18] Hip fractures cost $81,300 to $104,400 per patient[22] and total $25 billion in healthcare expenditures.[22] Many patients become debilitated. Thirty-nine percent of patients require a long-term care facility[23] leading to another 237 days of institutionalization on average, in addition to the average 97-day stay for non-fracture patients.[22] These institutionalized patients spend 334 days, or 17% of their remaining lives, in nursing homes.[22] In addition, 17% of hip fracture patients die within 6 months and 25% by 1 year.[22] About 4% die as inpatients[23] and 17% in nursing facilities.[22] People 65 or older have 86% of all hip fractures,[22] and this portion of the population is expected to double over the next 40 years.[22,24] Thus, the number of hip fractures and their associated impact will grow.

Etiologies of Hyponatremia

In the United States, the elderly are most susceptible to hyponatremia because of age-related changes, chronic disease, iatrogenic injury, diet, drugs, and idiopathic factors. The incidence

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of hyponatremia ranges from 7% in the ambulatory[1] to 53% in institutionalized geriatric patients.[3] As people age, the glomerular filtration falls as glomeruli become sclerotic.[25] Strokes, head trauma, and brain tumors lead to hypothalamic secretion of vasopressin, antidiuretic hormone (ADH) specifically, which increases water reabsorption in the kidneys, diluting the serum sodium concentration.[26] Congestive heart failure and cirrhosis increase ADH levels, reducing the ability to dilute urine, and causing hypotonic hyponatremia.[27] Paraneoplastic syndromes are also associated with autonomous production of ADH, causing the syndrome of inappropriate secretion of ADH (SIADH).[4] Third-spacing of fluid after surgery decreases effective arterial blood volume, stimulating ADH secretion and inducing hyponatremia.[2] Hypothyroidism and hypocortisolism are known causes, too.[28] Patients with low-salt, low-protein diets, have the "tea-and-toast syndrome," an impaired ability to excrete water, because of reduced solute availability.[29] Thiazides and furosemide promote sodium excretion; however, thiazides are more often associated with hyponatremia, as they do not interfere with generation of a hypertonic renal medullary interstitium and are therefore, more often associated with inappropriate urinary concentration.[30] Non–steroidal anti-inflammatory drugs inhibit prostaglandins, causing vasoconstrictive reductions in the glomerular filtration rate and increased ADH action. Last, psychotropic medications, selective serotonin reuptake inhibitors, produce an SIADH-like state.[1,2]

Clinical Evidence

A 2002 retrospective clinical study by McPherson and Dunsmuir[8] was the first to report the incidence of MCH (sodium, <130 mmol/L) in patients with a hip fracture. Of 107 patients (mean age, 79.1 years; range, 37-101 years), 3 (2.8%) were hyponatremic (sodium, 125-130 mmol/L) when they presented with a hip fracture. The study did not find a causal relationship between hyponatremia and fracture, and it underestimated the incidence of hyponatremia, missing patients with sodium levels between 130 and 135 mmol/L. Since then, the reported incidence of MCH has been as high as 26.5%.[16]

A 2006 case-control study by Renneboog and colleagues[10] re-emphasized that MCH (sodium, <132 mmol/L) is not asymptomatic, as its eventual consequences include falls, unsteadiness, and cognitive impairment. The study examined the incidence of falls in 122 patients (mean age, 72 years; SD, 13 years) with MCH (mean sodium, 126 mmol/L; SD, 5 mmol/L) and 244 age- and sex-matched normonatremic patients (mean sodium, 139 mmol/L; SD, 2 mmol/L) who presented to the emergency department. Twenty-six (21.3%) of the hyponatremic patients and 13 (5.3%) of the normonatremic patients fell (adjusted odds ratio [OR], 67.43; 95% CI, 7.5-607; P<.001). Incidence and OR were both underestimated, as hyponatremia was defined as a sodium level of less than 132 mmol/L.

Renneboog and colleagues[10] then studied volunteer patients who had SIADH and underwent gait and attention tests while hyponatremic (mean sodium, 128 mmol/L; SD, 3 mmol/L) and again while normonatremic (mean sodium, 138 mmol/L; SD, 2 mmol/L). The patients had 30 cm more deviation on gait analysis (P = .003), 75 ms more latency on attention testing (P = .001), and 40 more attention errors (P = .003) when they were hyponatremic than when they were normonatremic. Long-bone fractures caused by a fall seem to be related to hyponatremia–induced gait instability and attention deficits; the threshold for gait deficits is 134 mmol/L, and for attention deficits is 132 mmol/L.[11] Slow nerve conduction is thought to cause these deficits: low extracellular sodium concentration results in a low electrochemical gradient and thus weak sodium-dependent depolarizations.[31] In the final part of the study by Renneboog and colleagues, 10 volunteers were tested before and after ingesting alcohol (mean blood alcohol level, 0.6 g/L; SD, 0.2 g/L); however, the inebriated volunteers had fewer attention and balance impairments than the hyponatremic SIADH volunteers did.

In 2008, Gankam Kengne and colleagues[11] suggested that hyponatremia (sodium, <135 mmol/L) is a major independent risk factor for fracture from an incidental fall. In their case, control study, 67 (13.1%) of 513 ambulatory elderly (mean age, 81 years; SD, 8 years) with a fall-related fracture were hyponatremic (mean sodium, 131 mmol/L; SD, 3 mmol/L) at time of presentation. Only 20 (3.9%) of 513 age- and sex-matched non-fracture controls were hyponatremic. The adjusted OR for hyponatremia-associated fracture was 4.16. The authors speculated that they too underestimated the data; the BMD, body mass index, and electrolyte data were incomplete. However, their data were corroborated in a 2012 retrospective case-control study by Tolouian and colleagues.[18] Of 249 elderly patients admitted with a hip fracture, 42 (16.9%) were hyponatremic (sodium, <135 mmol/L), compared with 2 (4.5%) of 44 control elderly patients, admitted for elective total knee or hip arthroplasty (P = .03). Hyponatremia was almost as significant a risk factor for fracture as old age (hyponatremia OR, 4.80; age OR, 5.57; 95% CI, 1.06-21.67; P = .04).

In 2009, Sandhu and colleagues[12] examined the incidence and etiology of hyponatremia (sodium, <135 mmol/L) in 364 elderly patients (mean age, 79.2 years; SD, 8.2 years) with a large-bone fracture (hip, pelvis, or femur). Thirty-three patients (9.1%) were hyponatremic (mean sodium, 131 mmol/L; SD, 2 mmol/L), whereas 15 (4.1%) of age- and sex-matched non-fracture controls were hyponatremic (P = .007). Nonetheless, hyponatremic patients were 2.5 times more likely to fracture (P = .01), independent of age and sex, and women were 1.6 times more likely to fracture (P = .01) than men. Notably, 8 (24%) of the fracture patients and none of the control patients were using antidepressants, adding another potential bias. The study did not differentiate between types of large-bone fractures and omitted small-bone fractures.

In 2010, Kinsella and colleagues[13] retrospectively analyzed a cohort of 1408 women (mean age, 61.4 years; SD, 10.7 years) who underwent dual-energy x-ray absorptiometry (DXA) measurement. The authors determined that hyponatremia (sodium, <135 mmol/L), independent of osteoporosis, was associated with fracture. Of the 1408 women, 632 (45%) had osteopo-

rosis, and 254 (18%) had a fracture in the past. Of those with a past fracture, 22 (8.7%) were hyponatremic during the DXA test, compared with 8 (3.1%) of those without a past fracture (P<.001). Moreover, the OR for a hyponatremic female to fracture was 2.25 (95% CI, 1.2-4.1; P<.01). Multivariate logistic regression analysis (controlling for age, chronic kidney disease, T-score, risk factors, and treatments) revealed MCH as a major independent risk factor for fracture, independent of osteoporosis. The authors cautioned against using thiazides for bone protection, stating that the positive calcium balance—as described by Bolland and colleagues[32]—may be offset in some patients by the consequences of hyponatremia. They reported that the incidence of hyponatremia differed from that found in prior studies because of the time between fracture and sodium measurement, the female-only population, and the younger study population.

In 2011, Hoorn and colleagues[17] analyzed hyponatremia, fractures, and BMD among patients within the Rotterdam study, a population-based prospective cohort study of people 55 or older. The authors were the first to publish a prospective population-based investigation on this topic, analyzing multiple measurements and outcomes in 5208 participants (61.5% female; age range, 70.3 years; SD, 9.1 years; mean follow-up, 7.4 years; SD, 3.3 years). Of these patients, 399 (7.7%) were hyponatremic (sodium, <136 mmol/L) at baseline (mean, 133.4 mmol/L; SD, 2 mmol/L). These patients were older (P<.001), fell one or more times per year (P<.01), had a higher incidence of type 2 diabetes mellitus (P<.001), and used diuretics more often (P<.001). Moreover, these patients were at increased risk for fracture (adjusted hazard ratio [HR] for nonvertebral fracture, 1.39; 95% CI, 1.1-1.7; P = .004). This increased risk was independent of disability, diuretic or psycholeptic medication, recent falls, and diabetes mellitus.

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Perhaps most concerning, the hyponatremic patients in the Rotterdam study[17] had a higher rate of all-cause mortality (P<.001), with an adjusted HR of 1.21 (95% CI, 1.2-1.6; P<.001), for the given study period of 12 years. The data confirmed the HR first published in a 2006 prospective observational study by Lewis and colleagues,[9] who reported that, of 2963 consecutive hip fracture patients, 592 (20%) were hyponatremic (sodium, <135 mmol/L), and had a 30-day mortality HR of 1.4 (95% CI, 1.1-1.8; P<.05). Hoorn and colleagues[17] suggested that the increased risk for death underestimates the number of fractures because patients die before they sustain a fracture. In addition, hyponatremia is a risk factor for fracture and death, but they questioned the causality of hyponatremia, suggesting it is a surrogate for another, unidentified process. As only baseline sodium values were measured, Hoorn and colleagues[17] did not know if hyponatremia was chronic or transient. Nonetheless, their data are significant.

These studies suggest that MCH is not benign, as previously thought. MCH causes gait instability and attention deficits, which lead to falls and fracture, independent of osteoporosis, age, and sex. In addition, MCH is almost as significant a risk factor for fracture as old age is, and these patients have higher all-cause mortality.

Basic Science and Animal Studies

The relationship between sodium and bone was described more than a century ago.[33] Recent clinical data[8-13,16-18] have once again generated interest in related basic science studies. In 1894, Gabriel[33] was the first to determine that the amount of sodium in chloride-free bone residue exceeds the amount associated with chloride only. The extra sodium, as Harrison[34] described it, was eventually understood to be associated with bone. In the 1950s, Bergstrom and colleagues[35-37] determined that, of total body sodium, 50% is in the extracellular milieu, whereas 20% is intracellular, and 30% is sequestered as an osmotically inactive calcium carbonate complex salt in bone. However, bone can be sacrificed to liberate stores of inactive sodium, maintaining homeostasis. Edelman and colleagues[38] estimated that 40% of bone sodium is exchangeable with radiolabeled extracellular sodium in 24 hours. In addition, Bergstrom and Wallace[36] found that rats with chronic sodium deprivation have a 50% drop in bone sodium in 2 weeks.

In 2010, Verbalis and colleagues[14] demonstrated direct causality between hyponatremia and decreased BMD. Desmopressin acetate, a synthetic form of vasopressin, was infused into rats for 3 months. Some rats were fed a liquid diet to induce hyponatremia (mean sodium, 110 mmol/L; SD, 2 mmol/L), whereas controls were fed a solid diet and remained normonatremic (mean sodium, 141 mmol/L; SD, 1 mmol/L). The 3 months of hyponatremia caused a 30% (P<.001) reduction in BMD of the excised femurs. This reduction was larger than in other models of osteoporosis in rats: oophorectomy (12%-17%),[39,40] vitamin D deficiency (12%),[40] and orchiectomy (6%).[41] Histologically, and with micro computed tomography, hyponatremia reduced cortical and trabecular bone: volume decreased by 30% to 70% (P<.001), trabecular number declined by 60% to 80% (P<.001), cortical thickness shrunk by 40% to 60% (P<.001), trabeculae separation increased 3-fold (P<.01), and osteoclast number increased 5-fold (P<.01). There was also decreased serum osteocalcin (P<.05), signifying decreased bone formation.

Later, Barsony and colleagues[15] showed the cellular and molecular mechanisms involved in hyponatremia-induced osteoclastogenesis (ie, osteoclast progenitor stimulation and differentiation). A dose-dependent relationship exists between

hyponatremia, osteoclast number, and resorptive activity. Osteoclasts grown in hyponatremic media were larger and contained more nuclei and interconnections. These changes were significant after just 3 days in culture ($P<.05$) and maximal after 11 days ($P<.001$). The dose-dependent sodium/ascorbic acid transporter is a possible mediator of hyponatremia on osteoclasts.[15] Low levels of extracellular sodium decrease ascorbic acid uptake, enhancing osteoclastogenesis. In addition, low intracellular levels of the antioxidant ascorbic acid allow free radicals to accumulate within cells, including osteoclasts, causing DNA damage and oxidative stress. The cellular injury was proportional to the degree of hyponatremia.

Data from the Third National Health and Nutrition Examination Survey (NHANES),[42,43] a database of United States population health information, showed a positive linear correlation between hyponatremia and decreased BMD.[15] MCH was associated with a 14.7% reduction in BMD at the hip. It was expected that, for every 1-mmol/L decrease in sodium, hip BMD would decrease by 0.037 g/cm^2, and the adjusted OR for a hyponatremia-induced osteoporotic femoral neck was 2.87 times higher than for normonatremic adults (95% CI, 1.41-5.81; $P = .003$).

Thus, new research is beginning to demonstrate causality between hyponatremia and decreased BMD and also to unlock the cellular and molecular mechanisms involved in hyponatremia-induced "osteoclastogenesis." In addition, research suggests that hyponatremia-induced free radicals may also injure other organs.

Current Perspectives and Future Directions

Although the causative effect of hyponatremia on bone metabolism is becoming evident, when and how hyponatremia should be treated are unanswered questions that require screening, monitoring, and treatment protocols. Most investigators advocate routinely monitoring patients for MCH, so that appropriate workup and treatment can be initiated.[6,9-14,17,18,44,45] However, there is no universally accepted definition of MCH, and the true incidence of MCH, somewhere between 2.8%[8] and 26.5%,[16] has not been determined. What values constitute mild? How long is chronic? How do physicians examine for the subtle signs and symptoms? For now, there are more questions than answers.

According to Barsony and colleagues,[19] hyponatremia exacerbates senescence in rats: hypogonadism, decreased body fat, skeletal muscle sarcopenia, and cardiomyopathy. However, our understanding of MCH in humans is incomplete, and clinical results are unknown. Most physicians aggressively treat hypokalemia, hypophosphatemia, hypomagnesemia, and/or hypocalcemia regardless of severity, whereas asymptomatic hyponatremia seems to invoke less urgency and is not treated until symptoms arise.[5,18] Multiple options for treatment, reviewed elsewhere,[46-49] might be appropriate beyond discontinuing culpable drugs: fluid restriction, salt tablets, furosemide, hypertonic saline, and the recently developed vasopressin-receptor antagonists, such as tolvaptan. In the rat, Barsony and colleagues[19] found that excessive doses of vitamin D stopped hyponatremia-induced effects on bone. The culpable drugs and their side effects have not been identified, either. Chow and colleagues[50] recently suggested (after performing multivariate analyses) that there is no fracture risk with thiazide-associated hyponatremia. Last, are the risks reversed once hyponatremia is treated?[44] At what point are the effects permanent? Is there such a thing as mild transient hyponatremia? Many clinical and epidemiologic questions remain.

Physiologic questions are also unanswered. More research is needed to further elucidate these phenomena, especially in humans. Some believe[17,45] that hyponatremia is a surrogate marker of an unidentified disease or risk factor because fracture risk in hyponatremic patients is independent of BMD, and these patients have a higher mortality rate, with HRs ranging from 1.21 over a 12-year period[17] to 1.4 over a 30-day period.[9] For example, Hoorn and colleagues[17] explained that patients with diabetes mellitus not only have hyperglycemia-induced hyponatremia but also higher fracture risk despite higher BMD. This finding may be a consequence of diabetes-induced cardiovascular disease, peripheral neuropathy, and retinopathy leading to poor balance and increased fall frequency.[51]

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However, hyponatremia may have unidentified consequences (exacerbating senescence) rather than be a consequence itself.[19] As hyponatremia increases fracture risk independently of BMD, there may be an unknown factor influencing bone quality. Is there increased trabecular microfractures or decreased repair? Does hyponatremia-induced formation of free radicals play a role? How do hyponatremia and hypo-osmolality influence osteoblasts and collagen composition? In addition, the degree of MCH and the duration of MCH needed to effect clinically significant loss of bone quality and quantity have not been determined. Moreover, which bones are most susceptible to reduced BMD and fracture? And why? Finally, researchers may need to expand their questions beyond hyponatremia and also investigate hypernatremia and increased sodium intake as a cause of bone loss. As sodium and calcium reabsorption in the proximal renal tubule are related, increased dietary sodium intake causes calciuria.[52] Bone is sacrificed to replenish excreted calcium. New questions arise with each additional study, leaving more questions than answers, particularly regarding how hyponatremia affects human physiology.

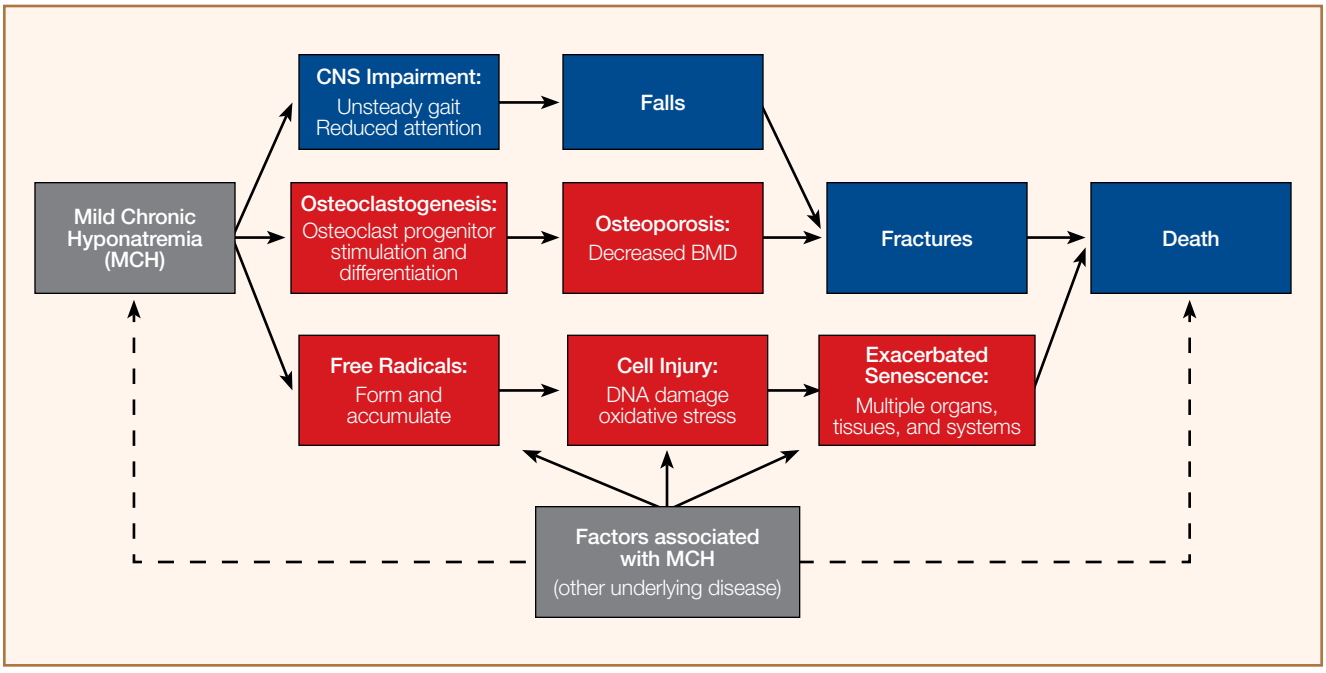

Figure. Proposed relationship between mild chronic hyponatremia (MCH) and bone injury. Blue boxes indicate possible cascade of events in humans with MCH. Red boxes indicate possible consequences of MCH in animal models. Dotted arrows show another possible mechanism, indicating that other unknown factors produce these effects and that MCH is a surrogate marker of other unidentified diseases or disease processes. Adapted with permission.[6,45] Abbreviations: BMD, bone mineral density; CNS, central nervous system; MCH, mild chronic hyponatremia.

Conclusion

Orthopedic surgeons should not take MCH lightly and leave it to their internists. An orthopedic surgeon may be the first physician to encounter and diagnose a patient's MCH, and thus can play a role in minimizing its orthopedic complications. Emerging studies disprove the traditional view that MCH is benign, as it causes impaired cognitive function and/or osteoporosis, leading to falls and fractures, and is associated with increased mortality and perhaps exacerbated senescence (**Figure**). Although the evolution of this concept cannot be traced in the orthopedic literature, orthopedic surgeons must be cognizant of the pathologic effects of MCH to properly educate patients and referring physicians. An opportunity exists for orthopedic surgeons to help define screening, monitoring, and treatment protocols and to further the understanding of the molecular and physiologic processes governing the effect of MCH on bone. MCH can account for a significant portion of the remaining unrecognized fracture risk. According to some,[14] reversal of calcium and vitamin D deficits, antiresorptive therapy, and correction of hormonal abnormalities could reduce fracture risk in only 50% of cases. The remaining risks are unknown, but MCH may be directly or indirectly involved.

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This paper will be judged for the Resident Writer's Award.