One quarter of this country, situated between western and eastern Europe, lies north of the Arctic Circle. It has three frontiers: to the southwest a maritime frontier involving the Gulf of Bothnia; to the north a settlement territory, that includes Lapland, and referred to as a land of midnight sun, where continuous daylight in summer gives way to months of darkness in winter; and an eastern land frontier that abuts Russia. It is a land of 10,000 islands and 10,000 lakes - consequences of the Ice Age that seems to repeat itself annually. Environmental controls are a national priority. For Finland, it is a balancing of seascape, lakescape and landscapes.

Grey-eyed Nicole Saarinen, resident in medicine, was also a dedicated environmentalist who enjoyed her country's flora and its fauna of elk, mink, marten and lynx. Sunday afternoon, July 7, 1991, found Nicole homeward bound to Oulu with Aalto, her trusty Spitz, at her side. She had spent the weekend swimming in the Saimaa Lake System: sauna baths were invigorating. Enjoying the panorama provided by coniferous forests, farms and lakes, she was reminded of the importance of wood and water and yes even winter - major components of Finland's economy, such as wood processing for plywood, pulp and paper and the designing/building of ice breakers - not an appliance found in one's ice box. Farmlands featured rows of crops, like barley, separated by strips of sod to restrict water movement, retain moisture and contain offsite damage by displaced soil. In Nicole's mind there appeared an aerial image of the land's topography created by contour strip-cropping and roadways. It was reminiscent of trabecular and cortical bone she thought. Only months ago bone histomorphometry, together with double tetracycline labeling, had proven useful in the evaluation of her patient with metabolic bone disease of uncertain etiology.

It was a typical cold, dark winter day in February when Mrs. K., a 62 year old Lapp living in Finland's frozen tundra, had presented to Nicole's clinic with recent onset, disabling back pain; no known prior illnesses. However, unlike most Finns living in Oulu, Mrs. K. had darker skin, straight dark hair and was only 145 cm (4 ft 10 in) tall. Were these clues? Was her stature related to her heritage or an acquired disorder? Did her dark skin and limited exposure to sunlight offer insights? Thoracic spine pain was the only physical finding while serum creatinine, calcium, phosphorus, protein electrophoresis and thyroid/parathyroid hormones were all normal; alkaline phosphatase was mildly elevated. Crush fractures of lower thoracic vertebrae were found on X ray. Nicole formed her differential diagnosis and ordered an iliac crest biopsy. Tissue did not reveal abnormally thick osteoid or low mineral apposition rate thereby excluding osteomalacia.

Instead, there was marked atrophy of trabecular bone with normal compact cortex. Nicole diagnosed Mrs. K. as having type I or postmenopausal osteoporosis and implemented hormone therapy in hopes of containing further erosion while promoting new bone formation. But how would she monitor Mrs. K.'s response? Serial bone biopsies were not an attractive option. How about serum alkaline phosphatase or urinary excretion of calcium or hydroxyproline, an amino acid specific to collagen, or bone mineral density by dual energy X ray absorptiometry. Mystified she collected her thoughts for Professor rounds.

Another patient had likewise piqued her curiosity on similar issues. Mr. J., a 45 year old former logger on the Kemijoki River, had recently worked at a fish factory. He presented with nausea, vomiting, malaise and jaundice. For years he had overindulged himself in a fermented beverage of malted barley; he now had hepatic failure that could not be attributed to other causality. Hepatic fibrosis, a dynamic and progressive remodeling process that constrains regenerating hepatocytes and often determines course and prognosis in alcoholic cirrhosis, had to be monitored. Serial liver biopsies were expected, but tissue morphology did...
not address fibrogenesis and was limited by sampling error. Biopsy was contraindicated when coagulation defect or infection were present. Nicole again wondered if noninvasive measures could not be used. What about standard liver function tests or serum proline?

Each of these questions drew Nicole’s attention to the basic sciences and their application to human investigation, where she could examine issues in more detail. But she recognized that even if she were forewarned by such information and therefore forearmed, could she forestall bone resorption or hepatic fibrosis? This would be her challenge.

Nicole was fortunate to have been selected to work in the distinguished laboratory of Leila and Juha Ristelli, Department of Medical Biochemistry at the University. There she would participate in studies that addressed the utility of various markers of extracellular matrix turnover in monitoring diseases of bone and liver and responses to pharmacologic intervention. It seemed Finland’s interests and her own concern for environment had drawn her to this topic. So had her patients, for it seemed no matter how many had awaited her in clinic, no matter how many were on her in patient service, no matter how seemingly straightforward their illness, calling on the next patient and deciphering their ailments – medical mysteries – was a fascinating challenge. Nothing was routine about the practice of internal medicine.

**Answer**

Interest in using tissue fluids to detect connective tissue turnover in diseased organs is attracting considerable attention. Of particular interest is the dynamic process of fibrillar type I and III collagen turnover in such organs – a balance between fibrogenesis and fibrolysis. Immunologic determination of serum carboxy- and amino-terminal propeptide concentrations, cleaved from type I and III collagens prior to fiber formation, is considered a promising approach to monitor collagen formation in several chronic diseases. Increased bone resorption accounts for bone loss in osteoporosis. Total alkaline phosphatase lacks sensitivity and specificity while its isof orm of bone reflects osteoblastic activity and bone matrix mineralization. The carboxyterminal propeptide of type I collagen (PICP), on the other hand, reflects matrix formation independent of subsequent mineralization. A pyridinoline cross-linked carboxyterminal telopeptide (ICTP) is a marker of bone matrix degradation by osteoclasts. Serum levels of PICP and ICTP have each been found to reflect skeletal bone formation and resorption, respectively, in patients with osteoporosis. Urinary excretion of calcium or hydroxyproline are not specific for bone turnover. Urinary excretion of ICTP is increased in postmenopausal women with osteoporosis. Monitoring bone turnover in response to intervention may prove useful, but the best management strategy to promote bone formation is presently uncertain. It has been suggested that the amino-terminal type III procollagen peptide correlates with the extent of fibrosis found on liver biopsy – a marker of active fibrogenesis particularly during early stages of fibrosis and which is not the case for serum proline levels or routine liver function tests. Pharmacologic intervention to halt hepatic fibrosis has not been clearly established.