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Perspective

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THE LONDON ATTACKS — A CHRONICLE

Improvising in an Emergency

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Thursday, July 7, 2005. A hot, humid day for London, and all the windows on the third floor of the British Medical Association (BMA) building are open. A last-minute change of plans at 9 a.m. leaves me working at BMA House, preparing for a meeting. This is to prove fateful.

9:20 a.m. Colleagues begin arriving. There is more than the usual commotion from emergency-services vehicles. Ten minutes later, an emergency medical helicopter from the Royal London Hospital is hovering overhead. Newsflashes on our computer screens report power surges and incidents on the London Underground. We turn on the television: clearly, a major incident is unfolding. A chill runs down my spine. I sat in the same place watching the events of 9/11.

Suddenly, around 9:50, everything momentarily appears pale pink. There is an enormous bang. Some of my colleagues have looks of terror on their faces. We can see white smoke and debris raining down in the square. The fire alarms are sounding.

Although staff members leave, the doctors stay, and we lower the blinds to give a modicum of protection from flying glass from any further explosion. After several minutes, we gingerly make our way to the front of the building and look down onto the stricken bus.

Within a second, I recognize that we are dealing with multiple blast injuries. I grab some surgical gloves and my ambulance service physician identity card — without it, we will be ignored by the London Ambulance Service.

On arrival downstairs, I meet the deputy chairman of the BMA Council, who is coordinating the first aid response. Knowing of my prehospital emergency care experience, he asks me to take over the direction of clinical operations while he requisitions and gathers resources. My assets are a building offering protection from all but a direct hit and 14 doctors, most of them experienced general practitioners with some training in emergency medicine. But we have no equipment, no communications, and no personal protective clothing. Armed with nothing, we set about maximizing the victims' chances of survival.

I have trained for such a situation for 20 years — but on the

assumption that I would be part of a rescue team, properly dressed, properly equipped, and moving with semimilitary precision. Instead, I am in shirtsleeves and a pinstripe suit, with no pen and no paper, and I am technically an uninjured victim. All I have is my ID card, surgical gloves, and my colleagues' expectation that I will lead them though this crisis.

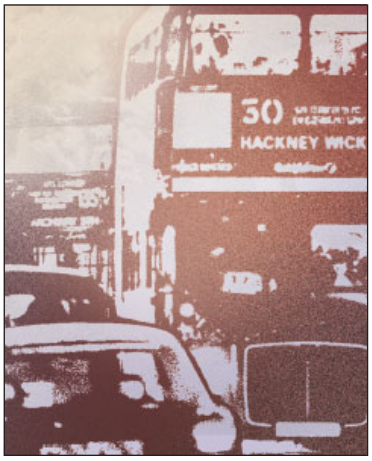
I gather my thoughts, try to remember the rules of triage and the principles of running a casualty clearing station (CCS). As specified by "The Plan," there are prompt sheets, but they are in my car 80 miles away. Until supplies arrive, we have nothing except bandages, chin lift, jaw thrust, and c-spine control.

My objectives are command, control, communication, coordination, and cooperation. Fail to achieve these, and we will have chaos — and lives will be lost needlessly. The aim is to get each patient to the right hospital in the right time frame. Our function is to triage, resuscitate, prioritize for transport, and feed patients into the rescue chain in an orderly fashion.

Gridlock means that it is 10:15 before we obtain limited ambulance service, supplies of oxygen, cervical collars, and IV-fluid sets. I find the most senior ambulance person present, since he should become the ambulance liaison officer, but he is occupied with clinical care and has no radio anyway. I can't communicate with the outside world.

I visit the nonwalking wounded, each of whom is being attended by a physician. Each physician is briefed to "remember the AcBCD [airway, cervical spine, breathing, circulation, disability] priorities, do the most for the most." Most of my colleagues have not cared for a casualty in 20 years. They accept my instruction without a murmur. Astonishingly, I have established command.

When I took over, I was told that there were eight priority 1, six priority 2, and seven priority 3 patients. I request that everyone be



moved into the courtyard: some victims are within 15 yards of the bus, and we still don't know whether there is a secondary device waiting to explode. I move to the gate to see whether there are more casualties to be brought in, but the police send me back inside until a controlled explosion has taken place.

I recount patients and find only 8 priority 1s and 2s and 7 priority 3s — a total of 15. Supplies are beginning to arrive in adequate quantities, and my colleagues are feeling less helpless, competently executing skills some have not practiced for decades. I ask someone to open the rear entrance and to arrange a one-way system around the courtyard so that ambulances can load and depart. The fire alarms are driving us crazy. They are disabled at my insistence, and a whiteboard is produced to chart patients' transition through the CCS. Control achieved.

Around 10:20, colleagues from the Royal London Hospital helicopter service arrive by car, and I give them a situation report that they communicate to their hospital. They give me various contact telephone numbers. I task them with looking at a victim who is being resuscitated, but their efforts are unproductive; the victim is pronounced dead at 10:40. Yet communications have been established.

An ambulance operations manager arrives. I give him a report, but already there is a discrepancy between my latest count and the one we reach as we jointly review the scene. Two priority 2 patients have been moved from the courtyard, and some priority 3 patients left when the rear doors were opened. This is not good news. I ask the helicopter medical crew to look at two priority 1 patients whose condition I have not reviewed and whose assigned physicians have, I suspect, reached the end of their skill repertoire. Coordination is evolving.

Triage labels arrive at 11:10. I brief colleagues on their use and assign one person to collect basic data on each victim and chart it on the whiteboard. Over the next 40 minutes, the remainder of our initial casualties are transported to hospitals in order of clinical priority.

At 11:45, the ambulance operations manager indicates that there are six casualties in the neighboring County Hotel awaiting transport. I suggest that they be

transferred by way of BMA House in order to avoid the potential danger of unexploded devices in Upper Woburn Place. Cooperation achieved.

We barely have time to retriage the patients before transportation to hospitals becomes available. Our CCS is cleared of all casualties by 12:10 p.m. Chaos averted.

Over sandwiches from the staff canteen, I brief my colleagues on the overall situation in the city and our specific situation and achievements. All but one victim who entered BMA House have left alive and in better shape than on arrival. I talk individually with colleagues, many of whom have nagging doubts about their performance.

Homeward transportation or overnight accommodation is arranged for all. I walk three miles to the nearest functioning train station. The train is air-conditioned, but there is no coffee. Normally, I would complain, but today's events have reminded me of what matters.

Many soon come to believe that the bombs were the work of religious extremists. I had counted at least eight different nationalities among the victims. My team consisted of Jews, Muslims, Christians, humanists, and agnostics, who all served humanity irrespective of race, color, or creed and regardless of personal danger. We had created a CCS in the shadow of a memorial to the physicians who served in the Second World War. I hope we did them proud.

On July 21, a memorial service is held in the courtyard, drawing an audience of 800. Members of the team are able to lay some of their ghosts to rest.

An interview with Dr. Holden can be heard at www.nejm.org

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THE LONDON ATTACKS — PREPAREDNESS

Terrorism and the Medical Response

Jim Ryan, M.Ch., D.M.C.C., and Hugh Montgomery, M.B., B.S., M.D.

Although Britain is no stranger to terrorist attacks, the pattern of activity has changed in recent years. Irish bombers first attacked London in 1867, but bombings peaked between 1969 and 2000, with 1972 alone seeing 1500 separate incidents — and 5005 casualties — in the United Kingdom. With the recent accessibility of information over the Internet have come new risks: in 1999, a single person used such information to construct and deploy three devices in central London, killing 3 people and injuring more than 120. The London attacks of July 7, 2005, however, represent a shift to a new scale and a new modus operandi.

At approximately 8:50 a.m. on that day, simultaneous explosions occurred below ground on three subway trains (see map). The first occurred some 100 m from the station platform at Edgware Road, killing seven persons at the scene. Within three hours, the nearest hospital had received 4 critically injured patients, 8 who were seriously hurt, and 14 with minor injuries. By the time the scene was cleared, at least 80 casualties had been triaged close to the scene, and the hospital had received 38. Of these, 24 were in critical or serious condition.

The second device exploded on the floor of the third carriage of a train, 200 m from the Aldgate station platform. More than 100 persons were wounded, 16 of them severely, and 7 died at the scene. Patients were triaged and transported (by ambulance and three buses) to the nearest hospital, which received 208 casualties from this and other sites, of whom 27 were admitted.

A third device exploded in the front carriage of a subway train between the King's Cross and Russell Square stations, through both of which evacuation occurred. Staff from two nearby specialist hospitals (the National Hospital for Neurology and Neurosurgery and Great Ormond Street Hospital for Sick Children) attended at the scene. Approximately 236 persons (36 of them severely injured) were transferred to local hospitals. Two adults were admitted to the Children's intensive care unit. Twenty-five people died at the scene.

Map Showing Sites of Explosions in London on July 7, 2005.

At 9:47 a.m., at Tavistock Square, a device exploded aboard a double-decker bus. Fourteen doctors, many from the nearby British Medical Association, provided immediate care. Thirteen persons died at the scene.

All told, four suicide bombers had left approximately 700 persons injured. Fifty-six of them (8.0 percent) were dead — a proportion identical to that after the train bombing in Madrid in March 2004, when 191 (8.0 percent) of the 2253 injured persons died.[1] In both attacks, most who died did so at the scene.

These parallels (many casualties, high mortality, and severe injuries) reflect the location and timing of the attacks. When an explosive device detonates, a small volume of explosive is rapidly transformed into a large volume of gas. A high-pressure blast wave expands outward at the speed of sound and, in interacting with the body, causes primary injuries (mainly at air interfaces such as the lung, ear, and bowel). The resultant blast wind propels solid matter into the patient (secondary injury) or the patient into solid matter (causing tertiary injury). Quaternary injury is caused by heat, flames, or the inhalation of smoke and hot gases. Confined spaces exacerbate such effects: surface reflections amplify and prolong the blast wave, the blast wind is channeled, and heat and gases are contained. The severity of injuries and the resultant mortality are thus greater.[2] The total number of persons endangered is increased by detonation within a rush-hour commuter environment.

Among the survivors, traumatic tympanic perforation was common. Secondary injuries, including penetration by biologic material, were frequent, as were traumatic amputation and smoke inhalation.

The attacks were unprecedented in scale and severity for London, but they were anticipated: the question, experts had said, was "not if but when." All the emergency services had prepared extensively for such attacks: in September 2003, our own hospital engaged in an all-agency response to a hypothetical explosion in a deep subway tunnel, and major exercises had been held only weeks before this event. For National Health Service facilities, preparedness is mandatory: chief executives are legally responsible for planning and practicing for conventional, chemical, nuclear, biologic, and radiologic attacks. Such intensive preparation is what permitted London's medical response system to work as well as it did.

Despite such planning and rehearsal, however, the attacks did present difficulties. First, the simultaneous detonation of devices at multiple locations put pressure

on emergency services. More than 100 ambulances were deployed by the London Ambulance Service, staffed by more than 250 professionals. The underground locations of some of the explosions added problems of site access and safety, as well as the need for specialist training and extrication skills. Working conditions were restricted, ventilation poor, temperatures high, and lighting problematic.

Second, the demand for communication among individuals and organizations after any major incident is amplified when multiple sites are involved. Moreover, the conventional communications infrastructure may fail at such times — telephone lines fail, and mobile telephone networks soon become overloaded by civilian use. Such breakdowns hamper communication between operational medical teams and their control centers and hospitals, and even mobile person-to-person communication within hospitals.

Finally, the targeting of the transportation infrastructure causes unique problems. The closing of bus and subway services leads to road congestion. At any other hour, such closings might have prevented medical and paramedical staff members from reaching their posts (but at the time of the bombing they were already there), as well as preventing the ready discharge of patients in order to clear beds. It may also hinder the rapid deployment of personnel to the scenes — a difficulty that was partially overcome by the (planned) deployment by the London Ambulance Service of paramedic crews on bicycles.

What, then, can we learn at this early stage? And what provision should we make for the future? Clearly, the nature of these bombings demonstrates the value of planning and rehearsal. Such preparation should recognize the changing nature of the threat.

Today, ready access to information on bomb construction facilitates the use of explosive devices by any number of aggrieved persons and organizations, and we should probably anticipate sporadic, smaller-scale attacks. In addition, the use of suicide bombers increases the difficulty of recognizing threats: one no longer seeks simply the classic unattended package. Biologic or chemical agents might be released at the time of a conventional blast, as sarin gas was released into the Tokyo subway system in October 1995. Furthermore, unlike other recent terrorist bombings against the United Kingdom, which generally targeted commercial property or military personnel, the attacks in London and Madrid targeted civilians, and the detonation of devices at multiple sites and in densely packed, confined areas increased the number of casualties and the severity of injuries.

Given these considerations, we should train individuals, in addition to undertaking regional or organizational preparations. If doctors are to assist meaningfully at the scenes of explosions, they should understand the workings of emergency services. Such training should not be restricted to a few "experts": many "passerby" doctors engaged in casualty care at each of the scenes. Specialists must be trained in new skills, such as extrication, triage, and transport. In London, a pool of such doctors — medical incident officers — already exists. The Royal London Hospital's helicopter emergency service, augmented by fast-response cars, can also deliver senior expert medical staff. On this occasion, 24 such senior staff were deployed.

Each city should review the provision of such services and ensure that training and equipment are adequate and that these professionals can function in a structured and reliable fashion. Sufficient numbers should be available, and their means of transportation — even when the standard infrastructure fails — ensured. All doctors should learn to recognize and meet the needs of blast victims: the unique mechanisms of explosive injury and the combinations of primary, secondary, tertiary, and quaternary lesions in one person are not encountered in any other situation.[3]

Above all, as the events of July 21 showed, we cannot be complacent. We must recognize that our future challenges may be far vaster in scale and that future attacks may be neither geographically nor temporally remote.

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THE LONDON ATTACKS — RESPONSE

Prehospital and Hospital Care

Julian Redhead, M.R.C.P., Patricia Ward, M.R.C.P., F.R.C.S.(Ed.), and Nicola Batrick, F.R.C.S.

On the morning of July 7, 2005, when four bombs were detonated on the London public transportation system, doctors were mobilized from all over the city to report to work and put their hospitals' major incident plans into action. Another, smaller group of physicians was mobilized by the Central Ambulance Control (the "gold doctors") to attend at the scenes of the explosions. These doctors included members of London's pool of "major incident officers" as well as members of the London Helicopter Emergency Medical Service.

Rapidly assembled at each bombing scene was a team of doctors who were experienced in delivering prehospital care. Working with the ambulance service, they fulfilled two roles: the care of the individual patients with serious injuries ("bronze doctors") and the management of the scene to evacuate large numbers of casualties to surrounding hospitals ("silver doctors").

Traveling to the scenes by road was difficult in the immediate aftermath of the bombings, although the police soon began to set up priority routes. Emergency medical helicopters moved bronze and silver doctors and their equipment to the scenes, flying more than 25 sorties.

At three of the scenes, emergency-services personnel worked in semidarkness, in an environment contaminated with smoke and debris. Decisions had to be made quickly regarding each patient's care; these decisions were necessarily affected by the resources available and the clinical condition of other patients requiring care.

What was striking was the relative quiet at the scenes. Despite the rapid and efficient deployment of emergency services, seriously injured patients, many of whom were fully alert, had to wait 30 minutes or more to be rescued from their frightening situations. Even in the face of such delays, however, the injured persons were seemingly all patient, dignified, and mutually supportive. Ambulant patients with relatively minor injuries had to wait even longer at the bombing sites. They, too, generally accepted these delays without complaint, allowing the receiving hospitals to concentrate on the more severely injured patients.

Although the bombing scenes quickly underwent a basic assessment for radiologic and chemical contamination, the possible presence of unexploded secondary devices remained a risk. Rescue efforts continued despite this risk, but awareness of it increased the pressure to minimize the time spent at the scenes.

At 9:20 a.m., St. Mary's Hospital, Paddington, was informed that a major incident had been declared. We had anticipated and had been readying ourselves for such an eventuality for some time. Now that it had happened, the hospital prepared to receive casualties, unsure of the number and nature of their injuries.

The major incident plan at St. Mary's has been activated on two previous occasions in the past six years — after the train collision at Paddington station in October 1999, when 51 casualties were treated, and after the Soho bomb attack in central London in April 1999.

On July 7, 2005, all staff members were called into the hospital. All patients who were in the emergency department were admitted to wards, transferred, or discharged home in order to clear the way for those injured in the bombings. Elsewhere in the hospital, the condition of inpatients was reviewed to assess the possibility of rapid discharge. Intensive care beds were identified. The operating rooms were prepared for emergency surgery.

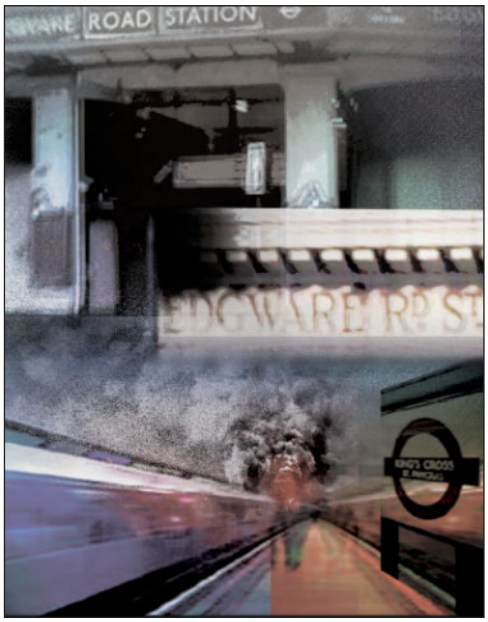
We deployed trauma teams to each of the four receiving bays in the resuscitation room and one to the operating room in the emergency department. Teams of pediatricians and pediatric anesthesiologists were standing by in our pediatric accident and emergency department.

The first casualties arrived at 9:50 a.m. The patients had mul-

tiple injuries, including traumatic amputations, burns, inhalation injuries, and chest and intraabdominal injuries — the expected pattern of injuries from a blast occurring in a confined space. The most striking feature of the patients who were less seriously injured was deafness due to the perforation of the tympanic membrane. Most patients were subdued and deeply distressed.

Patients were triaged on arrival by senior teams and assigned to one of three areas of the emergency department, depending on priority. When the condition of two patients deteriorated during their initial assessment, their priority was adjusted accordingly. After initial assessment and management, critically injured patients requiring surgery were transferred to the operating rooms, where teams of orthopedic, vascular, and general surgeons would work on into the night.

The repeated reassessment of all casualties was important. A senior surgical consultant reviewed all casualties, ensuring that a thorough secondary survey was performed. Orthopedic surgical expertise was fundamental in assessing patients with complex compound injuries and prioritizing cases for surgery. Ear, nose, and throat surgeons evaluated and arranged outpatient follow-up for all patients with audiologic consequences of the blast. Radiologists interpreted trauma x-rays and performed ultrasonography in the emergency department, as well as performing computed tomography. Chaplains, patient-liaison teams, and the mental health staff provided support to distressed patients and their relatives. Medical students acted as "runners" between key areas of the hospital and helped with supplies and blood samples.



Since St. Mary's is not a multidisciplinary, level 1 trauma center, we relied on the expertise of colleagues from neighboring hospitals, including ophthalmic surgeons and neurosurgeons. After patients with burns had received initial treatment and stabilization, our regional burn center took on those who required specialist burn care.

In addition to the treatment provided at St. Mary's, a team of appropriate staff members went to an adjacent hotel to attend to 50 priority 3 casualties from the bombing scene on Edgware Road.

During the course of the day, we were informed that an additional explosive device was thought to be located in the post office next to the hospital. This possibility caused understandable consternation among staff members and led to the temporary evacuation of some sites around the hospital.

In total, St. Mary's received 38 casualties (7 priority 1, 17 priority 2, and 14 priority 3) from the incident before finally receiving notification at 2:40 p.m. that the scene was clear. More than 200 staff members were involved in the initial response in the emergency department, working cohesively in challenging circumstances as they treated patients with injuries that we would not normally see in our civilian practices.

It is sobering to realize that in some parts of the world, civilians face violence on a regular basis. Those who provide the medical response in such ongoing or repeated crises have our respect and admiration.

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THE LONDON ATTACKS — AFTERMATH

Victimhood and Resilience

Simon Wessely, M.D.

At least until the failed attacks of July 21, the gut-wrenching shock of the July 7 suicide bombings in London had been starting to dissipate, and the nonstop news coverage was slowing. Gradually, Londoners were beginning to get on with their lives. Three days after the bombings, I joined the crowds celebrating the 60th anniversary of the end of the Second World War. The sun shone, and the Mall was full of old, proud men, wearing polished medals and fading berets. A military band gave a surprisingly good impersonation of the Glenn Miller Orchestra, and a Lancaster bomber accompanied by two Spitfires flew overhead, dropping poppies on us. The following day, England played Australia at cricket, and all seemed normal — including the resounding English defeat. True, there were more police than usual and we now had to enter the grounds by way of metal detectors, but the rituals of a London summer had returned.

But what about those for whom life as usual is not going to go on? Those whose lives have been shattered by bereavement and those whose bodies were shattered by the blasts of terrorist bombs? As one emergency worker told the BBC after leaving the scene of the bombing at King's Cross station, "I don't know what heaven looks like, but I now have a good idea of hell." Many of the survivors and the bereaved are suffering intense mental anguish, an anguish that is painful for the rest of us even to witness.

What can we do to help these people cope with the unimaginable? The conventional wisdom has been that those affected by such disasters need immediate psychological help to assist them in "ventilating" their feelings, to warn them of the emotional symptoms they may face in the coming days and weeks, and to prevent a subsequent breakdown. But though this belief may have been conventional, it was not wisdom.

There have now been more than a dozen controlled trials in which people who have been involved in accidents and other traumatic events have been randomly assigned to receive or not to receive such counseling. The results have shown conclusively that such immediate psychological debriefing does not work. Those who received it were no better off emotionally than those who did not. Worse, the better studies with the longer follow-up periods showed that receiving such counseling actually increased the likelihood of later psychological problems. In fact, the people who seemed to be harmed by this intervention were those who had been especially upset at the time — precisely those who one might think ought to be treated.[1] So whereas immediate post-trauma counseling may reassure the rest of us that something is being done, it does not actually help those who receive it.

Why doesn't it work? For some, such counseling is just too painful and comes too soon. It is also possible that warning people about potential symptoms makes them more likely to experience them. For some people, not talking is the most appropriate immediate response. Talking to a professional whom one has never met before and might not meet again may even get in the way of doing what comes naturally — talking with family members, friends, colleagues, religious advisors, or the family doctor. The people who know us best are likely to know what support we need and when we need it.

Asking people to talk about their feelings when they are still raw with pain is not always a good idea. The day after the bombing, all the television news bulletins showed footage of the father and the grandfather of 20-year-old Shahara Islam, who had gone to work on July 7 and hadn't been seen since. There we saw intense distress — the grandfather unable to articulate a coherent word, the father so distraught that it was uncomfortable to watch him. We didn't need to ask them how they were feeling. Five days later, it was announced that Shahara Islam had been killed in the bus explosion at Tavistock Square. Immediate counseling is not going to heal her family's grief.

Instead, what people need during the first few days is the support of their family and friends

and assistance with information, finances, travel, and the planning of funerals. The most appropriate immediate mental health interventions are practical, not emotional.[2]

Many people who are now in distress and despair will heal with time. Others will not, and serious psychological illnesses such as depression and post-traumatic stress disorder will develop in some. Prevention of these disorders would have required avoidance of the doomed trains. But the illnesses can be treated, and there are already plans to provide treatment.

Shortly after the blasts occurred, the National Health Service's mental health trusts covering the four hospitals that collectively treated 700 casualties from the bombings came together to coordinate their response. The Camden and Islington Mental Health Trust, which covers the area including University College and the Royal Free Hospitals, is taking the lead in organizing mental health services for those in need. About six weeks after the bombings, they will initiate a "treat-and-screen" program for people who were directly affected and are known to be at the highest risk for psychological sequelae. The delay is deliberate; some people will not be ready for interventions before then, and others will by then not need them.

Although the efficacy of mental health screening has not been established, it is a proportionate and reasonable response to initiate screening of those who were directly affected, especially given the known barriers to help-seeking among trauma victims with consequent mental health problems. There is good evidence that persons with ongoing stress disorders can benefit from cognitive–behavioral therapy. The real-life effectiveness of such screening and treatment was proved in the aftermath of the 1998 bombing in Omagh, Northern Ireland.[3]

But the events of July 7 also

demonstrated the sensible way in which ordinary people deal with adversity. We did not panic. We coped. That evening, I watched from my home in central London as an endless stream of people began their long walks home. They looked "inconvenienced rather than heartbroken," as one Web article (www.slate.com) put it. Ordinary people are tougher than we sometimes give them credit for being. And this should have come as no surprise. The people who were in the World Trade Center on September 11, 2001, had to find their own ways of leaving the buildings, and they did so without any signs of panic.

Indeed, people generally don't panic in the face of adversity — unless they are caught in confined spaces without any visible means of escape. One can understand the brief moments of overwhelming fear that some experienced when they were trapped in darkness after a bombing. One of our secretaries was on the train that was blown up under King's Cross. She said there was a moment of silence after the flash, followed by moaning and screams from the injured people in the front carriage. When black smoke began to drift into her carriage, some passengers did start to cry or panic. After a few minutes, however, most people regained their composure, and several got together to try to force open the train doors. During the 20 minutes or so that it took the emergency workers to check for chemical, biologic, and radiologic agents before descending to the train, she saw other passengers comforting the wounded and administering first aid.

One young man, named in media coverage simply as Paul, had lost his leg. The driver of the train tied his own belt around what remained of the leg, probably saving the man's life. While waiting for help, Paul told another passenger that there was a bright side: he could now enter

the Paralympics, he said, alluding to the previous day's announcement that London will host the 2012 Olympics — news that had been greeted with collective euphoria.

One reason for the stoicism demonstrated by so many Londoners is that although the atrocities of July 7 may have been the worst acts of terrorism to take place in the capital for many years, they were not the only ones we have seen. I remember the flash and boom of the bomb that was set off by the Irish Republican Army in 1992, destroying the Baltic Exchange. The collective memory of the city goes back even further. When Hasib Hussain detonated his bomb on the upper deck of the Number 30 bus and took 13 lives along with his own, he did so at Tavistock Square. A previous resident of that square was Virginia Woolf, and it was there that she returned one morning in October 1940, when the all-clear siren sounded, to find her house destroyed by German bombs. Her description of the scene foreshadowed those of the same square 65 years later.

Politicians, civic leaders, and the media have been keen on invoking the "Blitz spirit" in recent days, in order to foster resilience and remind us of our cultural scripts of defiance in the face of adversity. And there are resonances. Before the outbreak of the Second World War, politicians, military commentators, and emergency planners believed that aerial bombing would provoke mass destruction, panic, and a catastrophic collapse in morale. Yet these reactions did not occur. The Blitz killed 40,000 Londoners, and although there were short periods of considerable fear and disorganization, such a state was the exception, not the rule.[4]

But perhaps it would be more appropriate to compare our response to the July 7 bombings with the way we — and Israelis — have coped with living under the threat of terror.[5] Like the Israelis' immediate response, ours was to turn to our mobile telephones. Initial anxiety died down when we were able to determine the safety of those close to us, and if and when the current emergency resolves, we should expect our confidence in the transportation system to return as well. Moreover, the oft-rehearsed emergency plans worked: services were not overwhelmed, and people did their jobs well.

There is a danger that our stoicism, professionalism, and pride may become diluted over time. Almost immediately, reporters began carelessly describing London as "a city in trauma." Only 24 hours after the bombings, BBC Breakfast News was asking whether people who had only watched the scenes unfold on television would require counseling, and others demanded that counseling services be offered to all Londoners to enable them to "cope with the trauma." Such voices, however, were muted, and the messages coming from most mental health professionals were consistent, balanced, and less dramatic.

We must be careful to avoid shifting from the language of courage, resilience, and well-earned pride into the language of trauma and victimhood. The bombs made more than enough victims; it is important that we do not inadvertently create more.

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Rocky Mountain Spotted Fever — Changing Ecology and Persisting Virulence

J. Stephen Dumler, M.D., and David H. Walker, M.D.

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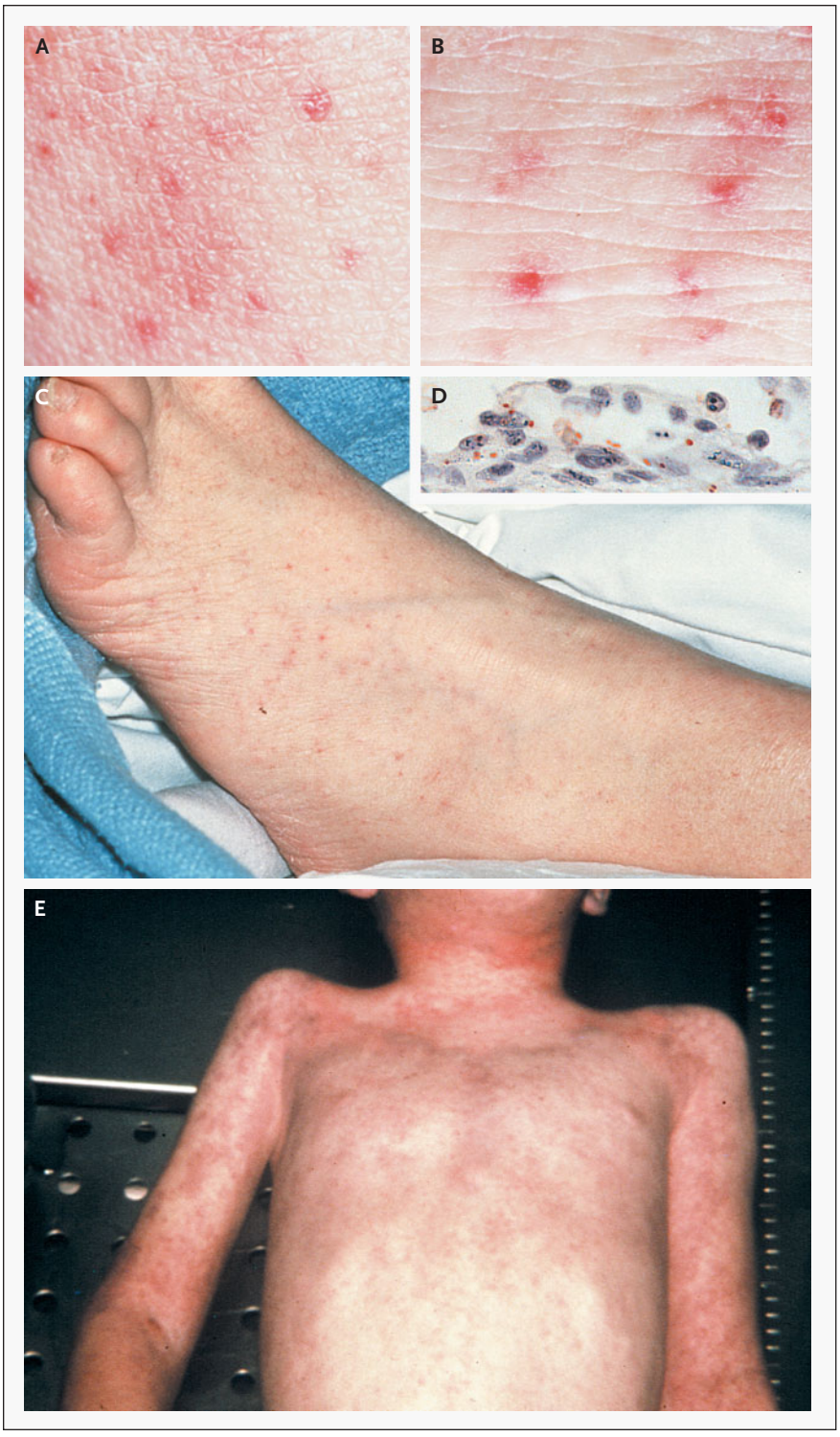
The explosive growth of emerging infections during the past 20 years has made it difficult to issue a call to arms about any pathogen with ecologic and epidemiologic features that are not conducive to a risk of dramatic regional or global spread. Such is the case with Rocky Mountain spotted fever, which is still one of the most virulent human infections ever identified. Nearly 100 years have elapsed since Howard T. Ricketts first described the pathogen transmitted by Montana ticks that killed up to 75 percent of the patients it infected. Despite a century of study, the causative bacterial agent is still reluctant to reveal its secrets, and no definitive virulence mechanisms have been identified. Infections are sporadic but persistent, with only small proportions of vectors infected, allowing many observers to assume that the disease is not a significant threat to human health. Yet 5 to 10 per 100 children and adults who are unfortunate enough to be infected will die, and many more will require intensive care and have sequelae such as amputation, deafness, or permanent learning impairment despite the availability of a simple and highly effective treatment.

Rocky Mountain spotted fever occurs when *Rickettsia rickettsii* in the salivary glands of a vector tick is transmitted into the dermis, spreading and replicating in the cytoplasm of endothelial cells and eliciting widespread vasculitis, hypoperfusion, and end-organ damage induced by vascular permeability, which is most dangerous in the lungs and brain. Diagnosis is difficult because of the nonspecific presentation of the disease; its symptoms include fever, headache, myalgia, and (usually after three to five days) a rash that evolves from macular to maculopapular to petechial (see figure). Organ-specific symptoms such as nausea, vomiting, abdominal pain, and cough confound diagnosis by distracting attention from systemic manifestations. Early clinical suspicion and empirical therapy are essential, since severe illness and death are associated with a delayed diagnosis, which can stem from an absence of rash or a presentation during a season with a low level of tick activity. Awareness of these risks is critical for the successful treatment of Rocky Mountain spotted fever.

In the United States, *R. rickettsii* is predominantly transmitted by the American dog tick (*Dermacentor variabilis*) and the Rocky Mountain wood tick (*D. andersoni*). Vertical transmission hinges on a tick with an infected ovary, which ensures infected tick progeny. However, *R. rickettsii* takes a substantial toll even on the tick, since few larvae emerge from eggs of ticks that carry the infection, and even fewer mature into adults. The alternative horizontal transmission depends on transient rickettsemia in nonimmune hosts, on which uninfected ticks feed, creating newly infected ticks to replace those that do not survive. Perhaps feeding adjacent to an infected tick also allows for the acquisition of *R. rickettsii* without the presence of infection in the host, a mechanism that is well demonstrated in viruses carried by mosquitoes.

Since tick species have distinctive ecologic features and feeding preferences among animal hosts, the transmission of Rocky Mountain spotted fever is in part determined by tick biology. For example, *Rhipicephalus sanguineus*, the brown dog tick, feeds predominantly on dogs in peridomestic habitats and is now recognized as important in the transmission of Rocky Mountain spotted fever to humans, as described by Demma et al. (pages 587–594). By virtue of this relationship, *R. rickettsii* transmitted by the brown dog tick presents a threat owing to unique epidemiologic features that differentiate it from the American dog tick (*D. variabilis*) that resides in rural and suburban regions with its small mammal hosts. It is not known to what degree various tick vectors, such as *Amblyomma cajennense* and *A. aureoloatum*, along with their specific ecologic features and hosts, determine the prevalence and incidence of Rocky Mountain spotted fever in Mexico, Central America, and South America. How other changing ecologic and environmental conditions affect the viability of ticks, the immunity and abundance of reservoir hosts, the prevalence of infection in tick populations, and the proximity to humans



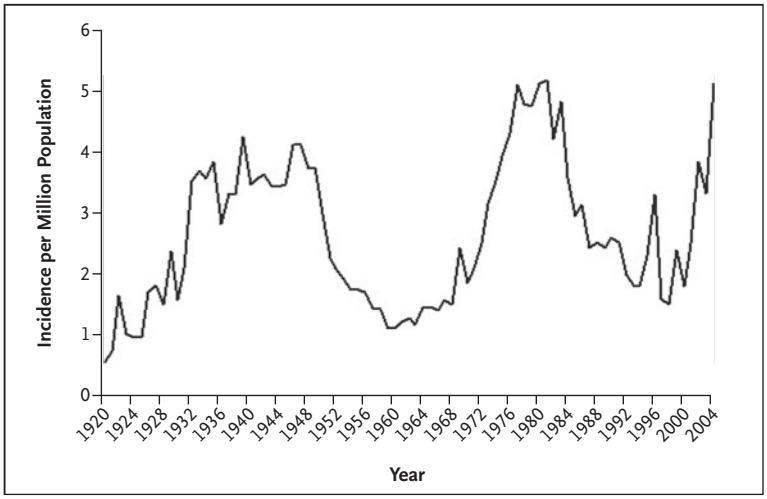
Evolution of Rash in Rocky Mountain Spotted Fever.

Most physicians are taught that the predominant rash of Rocky Mountain spotted fever is petechial. However, a spectrum of findings is more typical, including rashes that are initially macular or maculopapular (Panel A), petechial (Panels B and C), or purpuric, as seen in advanced or fatal disease (Panel E, courtesy of Grover Hutchins, M.D.). *Rickettsia rickettsii* can be seen in the endothelium of dermal vasculitic lesions by immunohistochemical analysis (Panel D).

are critical issues that require much more study.

Is it reasonable to worry about an infection that was reported in the United States in 1998 only 365 times and for which 0.5 percent of ticks or less are infected in areas of endemic disease? Considering that Rocky Mountain spotted fever is one of the oldest vector-borne infections known, the answer must be yes. The disease is in the midst of its third emergence since 1920, after peaks from 1939 to 1949 and again from 1974 to 1984 (see chart), yet the reasons for the cyclical waxing and waning are unknown. Previous theories that have attributed this phenomenon to suburban development, changes in recreational activities, or long-term changes in climate have not withstood careful investigation, and human exposure has only increased. Since the 1998 nadir, 1514 cases were reported in 2004, an increase by a factor of four to an absolute number higher than ever reported in U.S. history. The gravity of the situation is further weighted by the acknowledgment that the number of deaths from Rocky Mountain spotted fever is at least four times the reported number and that nonfatal cases — even those with severe sequelae — may be far more underreported.

Although Rocky Mountain spotted fever occurs only in countries in the Western Hemisphere — including Canada, Mexico, Costa Rica, Panama, Colombia, Brazil, and Argentina, where it is also reemerging after years of dormancy — rickettsioses caused by pathogens related to the spotted-fever group are also increasing worldwide, including in Europe, Asia, Africa, and Australia. The international toll of these infections is difficult to estimate,



Incidence of Rocky Mountain Spotted Fever in the United States since 1920.

but the relentless course of Rocky Mountain spotted fever in the United States suggests a similar effect worldwide.

The reasons for the underrecognition of Rocky Mountain spotted fever fall squarely on physicians and the system that educates and reeducates them. The nonspecific presentation of the disease makes diagnosis difficult. However, far too few physicians consider a diagnosis of Rocky Mountain spotted fever or take the time to inquire about tick bites or exposures — critical information that can lead to the diagnosis and to lifesaving empirical therapy with doxycycline. The laboratory is also a weak link. The most widely applied diagnostic tool, serologic analysis, is not useful during active infection, polymerase-chain-reaction analysis is insensitive, and immunohistochemical analysis of skin-biopsy specimens for *R. rickettsii* antigen is not widely or promptly available. No longer can we consider Rocky Mountain spotted fever a disease of only rural and southern venues; it has emerged and reemerged again. Only with careful education, clinical vigilance, and continued clinical, ecologic, and fundamental scientific investigation will the specter of Rocky Mountain spotted fever be controlled.

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THIS WEEK *in the* JOURNAL

ORIGINAL ARTICLE

Alendronate after Parathyroid Hormone (1–84)

Whether antiresorptive therapy is required to maintain gains in bone mineral density after treatment of osteoporosis with parathyroid hormone (1–84) is unknown. The investigators previously reported that concurrent treatment with parathyroid hormone and alendronate offered no advantage over monotherapy with respect to bone mineral density; they now report that the use of alendronate after treatment with parathyroid hormone maintains or increases densitometric gains.

SEE P. 555; EDITORIAL, P. 624

ORIGINAL ARTICLE

Alendronate Alone or with Parathyroid Hormone for Osteoporosis

Women with osteoporosis who had been taking alendronate for at least 1 year were randomly assigned to continued therapy with alendronate alone or with daily or cyclic parathyroid hormone (1–34) for 15 months. Indexes of bone formation rose quickly in both parathyroid hormone groups but declined during cycles without parathyroid hormone, increasing again with the resumption of treatment. Bone resorption rose in both parathyroid hormone groups, more with continuous than with cyclic therapy. Cyclic administration of parathyroid hormone causes the early bone-formation, stimulating phase of therapy to be dissociated from the later phase (remodeling) and may have therapeutic implications.

SEE P. 566; EDITORIAL, P. 624

ORIGINAL ARTICLE

Prompt versus Delayed Insertion of Tympanostomy Tubes

In children younger than three years of age with persistent middle-ear effusion, prompt insertion of tympanostomy tubes, as compared with delayed insertion up to nine months later if effusion persisted, did not improve developmental outcomes in the children when they were six years old. These data support current recommendations not to routinely insert tubes in otherwise healthy children solely on the basis of a persistent middle-ear effusion.

SEE P. 576; CME, P. 642

ORIGINAL ARTICLE

Rocky Mountain Spotted Fever and Brown Dog Ticks

An outbreak of Rocky Mountain spotted fever in rural eastern Arizona affected 16 patients, 2 of whom died. Dense populations of brown dog ticks were found at the patients' homes, and *Rickettsia rickettsii* was identified in those ticks. The investigation implicated the ticks as the vector of Rocky Mountain spotted fever, which raises concern about the potential of this common tick to transmit *R. rickettsii* in other settings.

SEE P. 587; PERSPECTIVE, P. 551

CLINICAL PRACTICE

Postmenopausal Osteoporosis

A 63-year-old woman presents with a history of acute low back pain. She had menopause at 44 years of age but never received postmenopausal hormone-replacement therapy. She reports a Colles' fracture at the age of 60. Her mother had a hip fracture at 70. Lumbar-spine films reveal a new vertebral fracture. Dual-energy x-ray absorptiometry of the hip shows a bone mineral density T score of –1.3. How should her case be managed?

SEE P. 595; CME, P. 641

MECHANISMS OF DISEASE

RXR Heterodimers in the Metabolic Syndrome

The principal abnormalities of the metabolic syndrome are abdominal obesity, atherogenic dyslipidemia, hypertension, insulin resistance, inflammation, and prothrombotic states. This review focuses on the retinoid X receptor (RXR) and its partners in the metabolic syndrome. RXR and its partners are nuclear receptors that function as ligand-dependent transcription factors. The ligands are lipids, and the system functions as a cellular lipid sensor. Agonists and inhibitors of these receptors are promising treatments for this widespread syndrome.

SEE P. 604; CME, P. 643

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

A Woman with Early-Stage Estrogen-Receptor–Positive Breast Cancer

A 58-year-old woman with cancer detected on mammography chose to undergo breast-conserving therapy. The tumor expressed estrogen and progesterone receptors and lacked *HER2/neu* amplification. The authors discuss management options for early-stage breast cancer, and new techniques that may help clinicians select optimal therapy.

SEE P. 617

The NEW ENGLAND JOURNAL of MEDICINE

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One Year of Alendronate after One Year of Parathyroid Hormone (1–84) for Osteoporosis

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ABSTRACT

BACKGROUND

Since the use of parathyroid hormone as a treatment for osteoporosis is limited to two years or less, the question of whether antiresorptive therapy should follow parathyroid hormone therapy is important. We previously reported results after the first year of this randomized trial comparing the use of full-length parathyroid hormone (1–84) alone, alendronate alone, or both combined. In the continuation of this trial, we asked whether antiresorptive therapy is required to maintain gains in bone mineral density after one year of therapy with parathyroid hormone (1–84).

METHODS

In the data reported here, women who had received parathyroid hormone (1–84) monotherapy (100 μg daily) in year 1 were randomly reassigned to one additional year with either placebo (60 subjects) or alendronate (59 subjects). Subjects who had received combination therapy in year 1 received alendronate in year 2; those who had received alendronate monotherapy in year 1 continued with alendronate in year 2. Bone mineral density at the spine and hip was assessed with the use of dual-energy x-ray absorptiometry and quantitative computed tomography (CT).

RESULTS

Over two years, alendronate therapy after parathyroid hormone therapy led to significant increases in bone mineral density in comparison with the results for placebo after parathyroid hormone therapy, a difference particularly evident for bone mineral density in trabecular bone at the spine on quantitative CT (an increase of 31 percent in the parathyroid hormone–alendronate group as compared with 14 percent in the parathyroid hormone–placebo group). During year 2, subjects receiving placebo lost substantial bone mineral density.

CONCLUSIONS

After one year of parathyroid hormone (1–84), densitometric gains appear to be maintained or increased with alendronate but lost if parathyroid hormone is not followed by an antiresorptive agent. These results have clinical implications for therapeutic choices after the discontinuation of parathyroid hormone.

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*The investigators for the Parathyroid Hormone and Alendronate (PaTH) study are listed in the Appendix.

N Engl J Med 2005;353:555-65.

With the approval of teriparatide, or human parathyroid hormone (1–34), two distinct classes of drugs became available for the treatment of osteoporosis. Antiresorptive drugs, such as the bisphosphonates, reduce bone resorption, whereas anabolic agents, such as teriparatide, primarily stimulate bone formation. However, it is not clear whether combining these therapeutic classes will improve efficacy. Two studies reported in the *Journal* in 2003[1,2] addressed that question in men and in postmenopausal women. One study,[1] of which the present report is an extension, involved full-length parathyroid hormone (1–84), and the other involved teriparatide.[2] Both reports indicated that the concurrent use of parathyroid hormone and alendronate offered no advantage over monotherapy in terms of changes in bone mineral density.[1,2] In fact, the concurrent use of alendronate blunted large parathyroid hormone–induced increases in trabecular bone mineral density.

The approval of teriparatide by the Food and Drug Administration for the treatment of osteoporosis was issued with the recommendation that therapy not last more than two years. However, there were no recommendations about what to do in the period after parathyroid hormone treatment. Observational studies in humans and studies in rat models suggest that gains in bone mineral density achieved with parathyroid hormone are lost if an antiresorptive agent is not administered after treatment.[3-6] The Parathyroid Hormone and Alendronate (PaTH) study was designed a priori to include a second year of therapy to test whether it is necessary to follow parathyroid hormone with a bisphosphonate in order to maintain gains in bone mineral density made during exposure to parathyroid hormone, as well as to address other questions with regard to two years of combination therapy with parathyroid hormone and alendronate. The present study examines this hypothesis in a controlled, double-blind, randomized, and prospective manner.

METHODS

Study methods, previously described,[1] are summarized here.

SUBJECTS

We recruited participants from four U.S. clinical centers: Bangor, Maine; Minneapolis; New York; and Pittsburgh. Postmenopausal women 55 to 85 years of age were enrolled if they had a T score for bone mineral density below –2.5 at the femoral neck, total hip, or spine or if they had a T score below –2 at one of these sites and at least one of the following risk factors: an age of 65 years or more, a history of postmenopausal fracture (vertebral or nonvertebral), and a maternal history of hip fracture. We excluded women who had ever been treated with bisphosphonates for more than 12 months or for specified shorter intervals in recent periods.

TREATMENTS

The treatments in this study were full-length parathyroid hormone (1–84) (100 μg daily [NPS Pharmaceuticals] by subcutaneous injection), oral alendronate (10 mg daily [Fosamax, Merck]), calcium carbonate (500 mg of elemental calcium [Tums, GlaxoSmithKline]), and a multivitamin containing 400 IU of vitamin D (Rugby Laboratories).

STUDY DESIGN

After a two-week run-in period, 238 women were randomly assigned to one of four treatment regimens for two years, as follows: parathyroid hormone in year 1 followed by alendronate in year 2 (hereafter referred to as the parathyroid hormone–alendronate group); parathyroid hormone in year 1 followed by placebo in year 2 (the parathyroid hormone–placebo group); parathyroid hormone plus alendronate in year 1 followed by alendronate in year 2 (the combination-therapy–alendronate group); and alendronate for two years (the continued-alendronate group). All participants received daily calcium and vitamin D. This report covers the entire 24 months of treatment. Parathyroid hormone or an injectable placebo was administered only during year 1.

The study medications were provided by NPS Pharmaceuticals (parathyroid hormone and matching placebo), Merck (alendronate and matching placebo), and GlaxoSmithKline (calcium). Supplementary funds for quantitative computed tomography (CT) were provided by Merck. Merck and NPS Pharmaceuticals provided (nonbinding) comments on one draft of the manuscript.

The study design, data accrual, and writing of the manuscript were managed entirely by the investigators, who hold the data. The study was implemented in all facets, including data collection and analysis, by the University of California, San Francisco, coordinating center. Except for one clinician (D. Bauer), who was responsible for reports

to the data and safety monitoring board, participants, clinicians, and investigators remained blinded to the study treatments.

EFFICACY OUTCOME VARIABLES

Areal bone mineral density (in grams per square centimeter) at the lumbar spine, hip, and distal one third of the radius was assessed with the use of dual-energy x-ray absorptiometry (Hologic QDR 4500A or Delphi densitometers) at baseline, 12 months, and 24 months. Volumetric bone density (in grams per cubic centimeter) and bone geometry in trabecular and cortical compartments were assessed with the use of quantitative CT at the spine (L1 and L2) and total hip in a subgroup of 204 patients.[1,7] Specific outcomes from quantitative CT included trabecular bone mineral density at the spine and total hip as well as cortical bone density, content (in grams), and volume at the total hip.

After an overnight fast, serum samples were drawn and stored (at −70°C) until they were assayed for N-propeptide of type I collagen (a marker of bone formation) and serum C-terminal telopeptide of type I collagen (a marker of bone resorption) in a central laboratory (by P. Garnero at Synarc, Lyon, France). The baseline and 12-month assays were performed simultaneously, and the assay at 24 months was performed separately.

ADHERENCE, SAFETY ASSESSMENT, AND ADVERSE EVENTS

Adherence to treatment was assessed by means of the return of unused cartridges (parathyroid hormone, year 1) and tablets (alendronate, years 1 to 2). Full adherence to treatment each year was defined as the use of study medication (pills or injections) for at least 11 of the 12 months of that year and as the use of at least 80 percent of the prescribed medications during that period.

Patients were questioned at each visit about adverse events, which were coded with the use of preferred terms from the *Medical Dictionary for Regulatory Activities* (*MedDRA*) and classified by a single clinician at the University of California, San Francisco, who was unaware of the treatment-group assignments. The preferred terms from *MedDRA* were categorized according to the types of adverse events anticipated on the basis of previous trials of parathyroid hormone[8] and alendronate[9,10]; the adverse events were also assigned to broader categories according to organ systems. These categories were then compared across treatment groups by the data and safety monitoring board and reviewed for this report.

STATISTICAL ANALYSIS

We attempted to follow all the women who underwent randomization for all study visits and procedures, regardless of their level of adherence to the treatment regimens. Analyses were performed according to the intention-to-treat principle unless otherwise stated. Means within treatment groups, 95 percent confidence intervals, and t-tests for the percent change from baseline to 24 months and from 12 months to 24 months in variables measured by dual-energy x-ray absorptiometry and by quantitative CT were used to assess the significance of changes within groups. Geometric means and 95 percent confidence intervals are shown for changes in bone markers. For the period from baseline to 24 months, two sets of comparisons were made: the first was between the parathyroid hormone–alendronate group and the other three treatment groups, and the second was between the combination-therapy group and the other three treatment groups. We also compared changes from 12 to 24 months between the two groups that received parathyroid hormone therapy alone in the first year (parathyroid hormone–alendronate vs. parathyroid hormone–placebo). For all comparisons, a significance level of 0.05 (not adjusted for multiple comparisons) was used, but the comparisons for which $P<0.001$ are generally noted in the text. A complete listing of the changes within groups and the differences between groups is given in the Supplementary Appendix (available with the full text of this article at www.nejm.org).

On the basis of standard deviations from the results at 24 months in a previous trial,[9] with a power of 0.90 and a significance level of 0.05, we expected to be able to detect a difference between any two treatment groups in areal bone mineral density of 4 percent at the spine and 2.4 percent at the total hip.

RESULTS

CHARACTERISTICS OF THE PATIENTS AND ADHERENCE TO TREATMENT

Baseline characteristics of the participants are shown in Table 1. There were no significant differences in baseline characteristics among the four treatment groups, with the exception of areal bone mineral density of the spine, which differed signif-

Table 1. Baseline Characteristics of the Women.*

Characteristic	Parathyroid Hormone–Placebo Group (N=60)	Parathyroid Hormone–Alendronate Group (N=59)	Combination-Therapy–Alendronate Group (N=59)	Continued-Alendronate Group (N=60)	P Value†
Age — yr	70.1±7.3	68.7±7.4	70.2±6.8	70.7±6.8	0.44
Age according to subgroup — no. (%)					0.46
50–59	7 (11.7)	8 (13.6)	5 (8.5)	2 (3.3)	
60–69	21 (35.0)	23 (39.0)	23 (39.0)	26 (43.3)	
70–79	27 (45.0)	24 (40.7)	28 (47.5)	24 (40.0)	
80–89	5 (8.3)	4 (6.8)	3 (5.1)	8 (13.3)	
Age at menopause — yr	45.8±7.2	47.5±5.6	47.2±7.2	48.4±5.1	0.17
Race — no. (%)‡					0.25
White	54 (90.0)	57 (96.6)	57 (96.6)	58 (96.7)	
Other	6 (10.0)	2 (3.4)	2 (3.4)	2 (3.3)	
Height loss since age of 25 yr — mm	−45.8±31.6	−34.7±22.4	−40.8±27.2	−34.5±25.3	0.07
Body-mass index§	25.9±4.3	25.4±4.9	27.1±5.6	25.1±4.5	0.13
Clinical fracture since age of 45 yr — no. (%)	27 (45.0)	30 (50.8)	30 (50.8)	25 (41.7)	0.65
Previous alendronate use — no. (%)	6 (10.0)	7 (11.9)	4 (6.8)	10 (16.7)	0.39
For >12 mo or >4 wk in last 12 mo	1 (1.7)	0	2 (3.4)	2 (3.3)	0.52
Areal bone mineral density on dual-energy x-ray absorptiometry — g/cm²					
Total spine	0.76±0.10	0.79±0.10	0.82±0.12	0.78±0.12	0.02
Total hip	0.71±0.10	0.71±0.09	0.74±0.08	0.71±0.09	0.23
Femoral neck	0.59±0.09	0.61±0.08	0.61±0.07	0.60±0.07	0.40
Distal one third of radius	0.55±0.08	0.56±0.07	0.57±0.07	0.55±0.07	0.70
Volumetric density on quantitative CT — g/cm³¶					
Total spine	0.17±0.02	0.18±0.02	0.18±0.03	0.18±0.03	0.49
Trabecular bone at spine	0.08±0.02	0.08±0.02	0.08±0.02	0.08±0.02	0.61
Total hip	0.21±0.03	0.21±0.03	0.22±0.03	0.22±0.03	0.38
Trabecular bone at total hip	0.07±0.02	0.07±0.02	0.07±0.02	0.07±0.02	0.96

* Plus–minus values are means±SD.
† P values were calculated with the use of the one-way analysis-of-variance method for continuous variables and the chi-square method for binary variables.
‡ Race was self-reported.
§ The body-mass index is calculated as the weight in kilograms divided by the square of the height in meters.
¶ Quantitative CT was performed in a total of 204 participants at three clinical sites.

icantly among the four treatment groups (P=0.02). A similar trend was not evident for volumetric bone mineral density of the spine.

A total of 223 patients (94 percent) completed the 24-month follow-up. During the first 12 months, 75 percent of participants fully adhered to treatment by injection and 81 percent to treatment with tablets. In the second year, 80 percent fully adhered to treatment with tablets. There were no significant differences in adherence according to treatment group.

TWO-YEAR CHANGES IN BONE MINERAL DENSITY

Over 24 months, areal bone mineral density at the lumbar spine increased significantly (P<0.001) in all four treatment groups (Fig. 1). The largest cumulative increase was seen in the parathyroid hormone–alendronate group (12.1 percent), and the smallest in the parathyroid hormone–placebo group (4.1 percent; 8 percent difference; 95 percent confidence interval, 5.6 to 10.3 percent). The increase in the parathyroid hormone–alendronate group was significantly greater than in the other three treat-

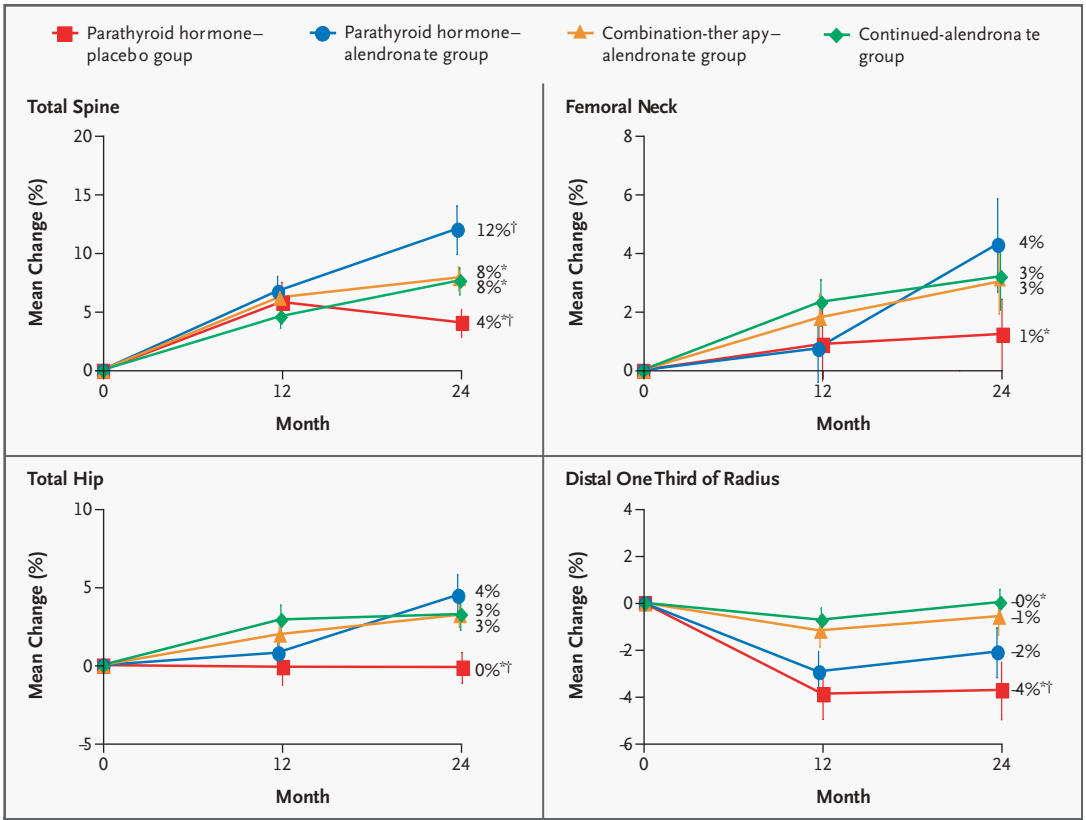

Figure 1. Mean Percent Changes from Baseline in Areal Bone Mineral Density at the Spine, Hip, and Distal One Third of the Radius, According to Treatment Group.

Bone mineral density was assessed with the use of dual-energy x-ray absorptiometry. An asterisk indicates P<0.05 for the comparison with the parathyroid hormone–alendronate group at 24 months. A dagger indicates P<0.05 for the comparison with the combination-therapy–alendronate group. The vertical lines represent the 95 percent confidence intervals for the changes at 12 and 24 months.

ment groups (P<0.001). The increase in the combination-therapy–alendronate group was significantly greater than that in the parathyroid hormone–placebo group (P=0.002), smaller than that in the parathyroid hormone–alendronate group (P<0.001), and similar to that in the continued-alendronate group.

At the femoral neck and total hip, there were significant increases (P<0.001) in areal bone mineral density over two years in all treatment groups except the parathyroid hormone–placebo group. Across treatment groups, the increases in the parathyroid hormone–alendronate group were significantly greater than those in the parathyroid hormone–placebo group (P=0.005 for the femoral neck and P<0.001 for the total hip).

Over two years, there were significant losses at the distal one third of the radius in both the parathyroid hormone–alendronate and parathyroid hormone–placebo groups (P<0.001 for both groups) but no significant changes in the other two treatment groups. The two-year cumulative loss in the distal one third of the radius in the parathyroid hormone–placebo group was significantly greater than in the parathyroid hormone–alendronate group (P=0.04), the combination-therapy–alendronate group (P<0.001), and the continued-alendronate group (P<0.001). The only other significant difference between groups at this site was that between the parathyroid hormone–alendronate group (–2.1 percent) and the continued-alendronate group (0 percent, P=0.006).

Volumetric bone mineral density in trabecular bone at both the spine and the hip increased in all

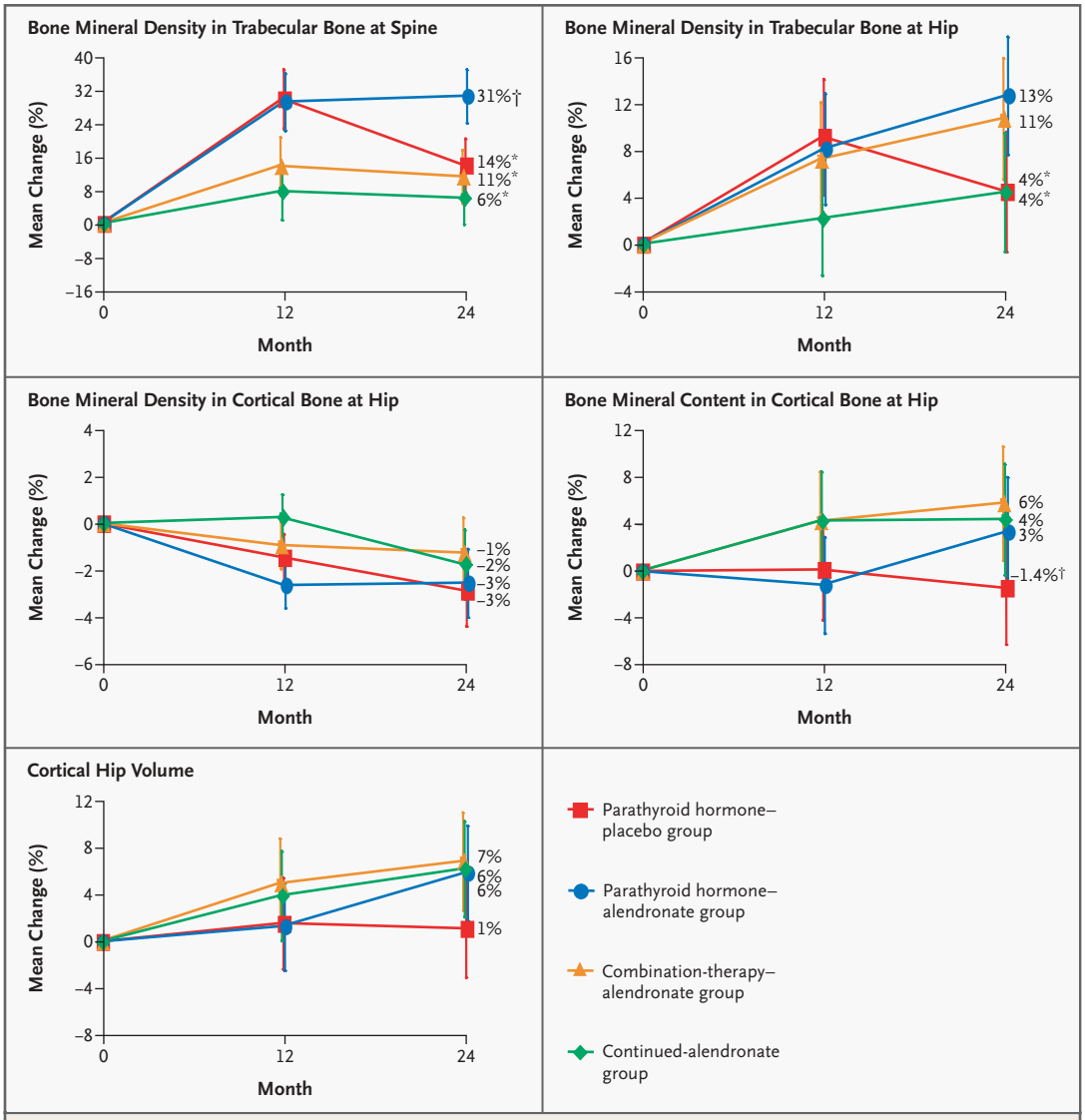

Figure 2. Mean Percent Changes from Baseline in Volumetric Bone Mineral Density and Cortical Measurements Derived from Quantitative CT at the Spine and Hip, According to Treatment Group.

An asterisk indicates P<0.05 for the comparison with the parathyroid hormone–alendronate group at 24 months. A dagger indicates P<0.05 for the comparison with the combination-therapy–alendronate group. The vertical lines represent the 95 percent confidence intervals for the changes at 12 and 24 months.

four treatment groups over the two years (Fig. 2). At the spine, the increases were significant (P<0.001) for three of the four treatment groups (the exception was the continued-alendronate group, P=0.06). The increase in volumetric bone mineral density at the trabecular spine was greatest in the parathyroid hormone–alendronate group (31 percent, P<0.001), which was significantly higher than in the other three groups (P<0.001 for all three comparisons). The increases in bone mineral density in trabecular bone at the hip were greatest in the parathyroid hormone–alendronate group (13 percent, P<0.001) and the combination-therapy–alendronate group (11 percent, P<0.001). In the parathyroid hormone–placebo group and the continued-alendronate group, the increases were smaller (about 4 percent) and not statistically different from baseline values.

Over the two years, in all four treatment groups, there were small declines in volumetric bone mineral density in cortical bone at the hip (changes of

–1 to –3 percent). The declines were significant in all treatment groups (P=0.02 to P<0.001) except the combination-therapy–alendronate group (Fig. 2). None of the declines differed among treatment groups. There was a trend toward an increase in the cortical bone mineral content and a significant increase in the cortical volume (P=0.004 to P=0.001) in all treatment groups except the parathyroid hormone–placebo group.

CHANGES IN YEAR 2

During year 2, among women in the parathyroid hormone–alendronate group, there was a significant additional increase in areal bone mineral density at the spine (4.9 percent, P<0.001) and hip (3.6 percent, P<0.001) (Fig. 3). In contrast, in the parathyroid hormone–placebo group, there was a significant decrease in areal bone mineral density at the spine (–1.7 percent, P=0.002) and no change at the hip or radius. The difference between further gains in year 2 in the parathyroid hormone–alendronate group and the decline in the parathyroid hormone–placebo group was significant at both the spine (6.6 percent; P<0.001; 95 percent confidence interval, 5.1 to 8.2 percent) and the total hip (3.6 percent; P<0.001; 95 percent confidence interval, 1.8 to 5.3 percent). During year 2, there were further increases in bone mineral density in trabecular bone at both the spine and the hip in the parathyroid hormone–alendronate group and decreases in the parathyroid hormone–placebo group (Fig. 3). At the spine, the decrease was almost 10 percent (P<0.001). The differences between the gains in the parathyroid hormone–alendronate group and the losses in the parathyroid hormone–placebo group in bone mineral density were significant in trabecular bone at both the spine (–13.3 percent; P<0.001; 95 percent confidence interval, –17.9 to –8.6 percent) and the hip (–10.1 percent; P=0.002; 95 percent confidence interval, –16.5 to –3.7 percent).

No significant change in volumetric bone mineral density in cortical bone was noted in either the parathyroid hormone–alendronate group or the parathyroid hormone–placebo group. However, there were increases in both bone mineral content (4.6 percent, P=0.05) and volume (4.4 percent, P=0.04) in cortical bone in the parathyroid hormone–alendronate group, with no significant changes in either factor in the parathyroid hormone–placebo group. However, neither the change in bone mineral content nor the change in volume during year 2 differed significantly between the two treatment groups.

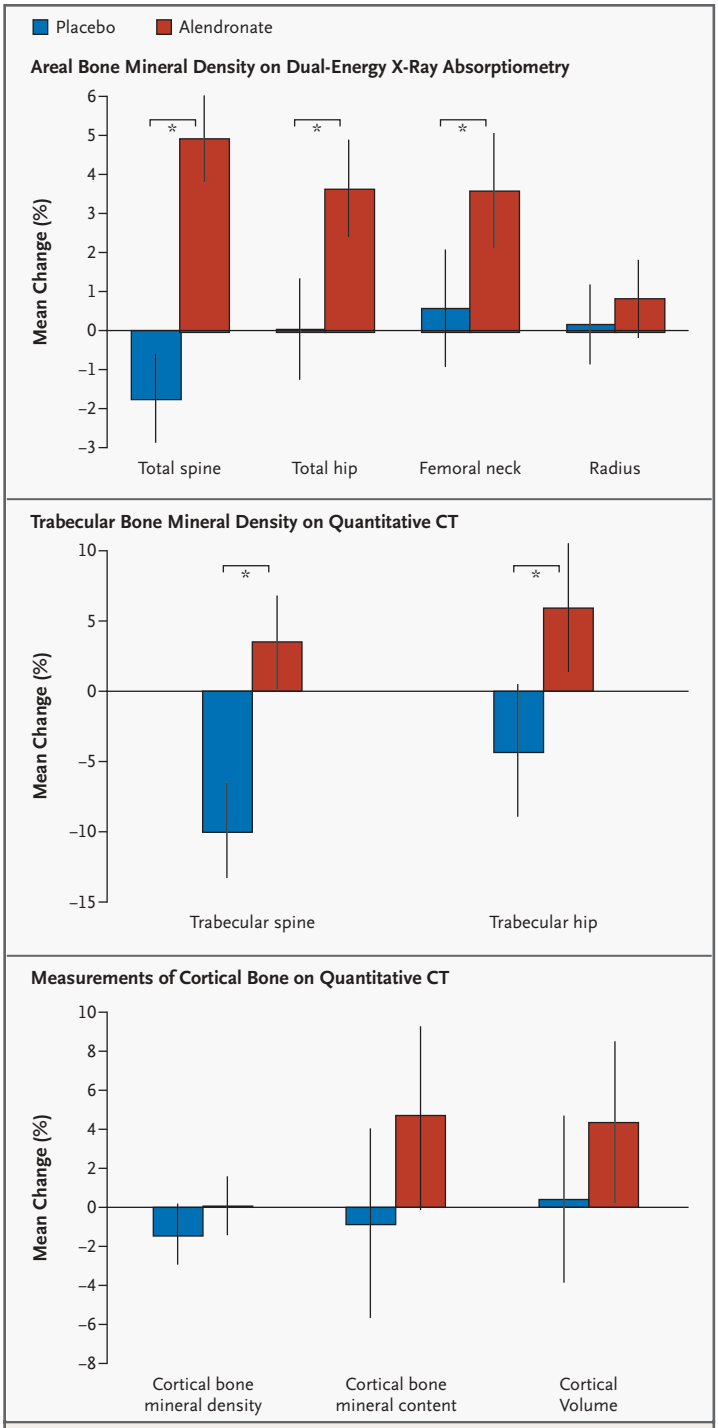

Figure 3. Mean Percent Changes during the Second Year after Cessation of One Year of Parathyroid Hormone Treatment in Women Treated with Alendronate and Placebo in the Second Year.

Changes in areal bone mineral density at the spine, hip, and distal one third of the radius, as measured by dual-energy x-ray absorptiometry, and in trabecular and cortical bone, as assessed by quantitative CT, are shown. The vertical lines represent the 95 percent confidence intervals for the mean changes. Asterisks indicate P<0.01.

MARKERS OF BONE REMODELING, FRACTURES, AND ADVERSE EVENTS

The increases in bone resorption and formation that had occurred as a result of parathyroid hormone therapy at month 12 had declined significantly by 24 months in the groups receiving parathyroid hormone in year 1 (the parathyroid hormone–alendronate, parathyroid hormone–placebo, and combination-therapy–alendronate groups) (Fig. 4). Despite large differences between the parathyroid hormone groups and the combination-therapy–alendronate group at month 12, women in both groups who received alendronate during year 2 had levels of biochemical markers of bone turnover below those at baseline; these values were indistinguishable from those in the continued-alendronate group. At 24 months, markers of bone turnover in the parathyroid hormone–placebo group had returned to baseline levels and were higher than in the other groups ($P<0.001$).

Over the two years, 21 women (8.8 percent) had one or more clinical fractures. The proportion of fractures did not differ among treatment groups. During year 2, a total of six women had a clinical fracture.

During year 2, there was no significant difference between the parathyroid hormone–placebo group and the parathyroid hormone–alendronate group in the occurrence of adverse events, serious adverse events, or adverse events associated with either alendronate (upper gastrointestinal events) or parathyroid hormone (nausea, vomiting, fatigue, headache, or reaction at the injection site).

DISCUSSION

This double-blind, randomized trial was designed to examine several combination-treatment options for previously untreated, postmenopausal women with osteoporosis. In the first year of the PaTH study, we found that combining parathyroid hormone (1–84) with alendronate did not provide a clear advantage over either form of treatment alone when the end point of bone mineral density (as measured by dual-energy x-ray absorptiometry and quantitative CT) was evaluated.[1] Moreover, the concurrent use of alendronate blunted the effect of parathyroid hormone on trabecular bone mineral density.[1] During the second year of the PaTH trial, we addressed several additional questions regarding sequential, rather than concurrent, anabolic and antiresorptive combination therapy. In particular, we tested the hypothesis that in order for densitometric gains to be maintained, parathyroid hormone therapy must be followed by bisphosphonate therapy. Results from the PaTH study support this a priori hypothesis by showing that gains in bone mineral density at both the spine and hip are much larger if parathyroid hormone monotherapy is followed by alendronate rather than no therapy. These data indicate that if antiresorptive therapy does not follow parathyroid hormone therapy, much of the

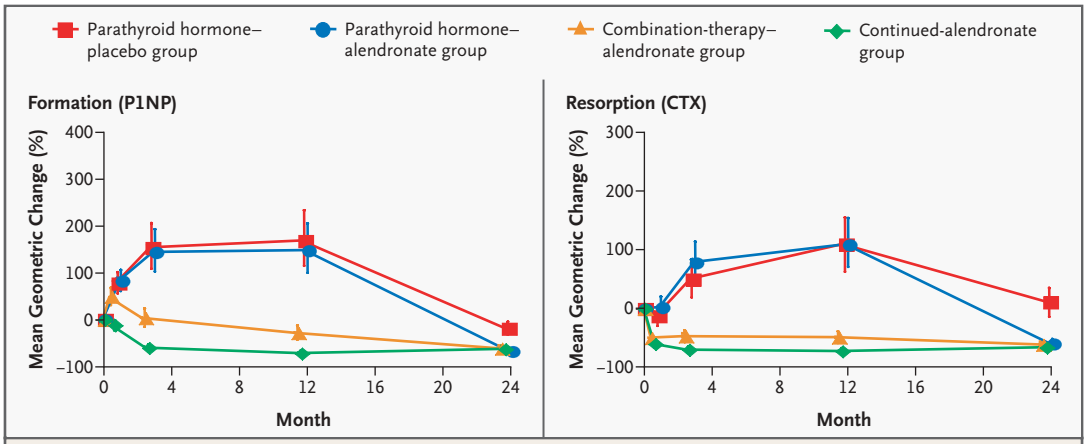

Figure 4. Mean Geometric Percent Changes from Baseline in Markers of Bone Metabolism, According to Treatment Group.

The changes are shown for N-propeptide of type I collagen (P1NP), a marker of bone formation, and for serum C-terminal telopeptide of type I collagen (CTX), a marker of bone resorption. The vertical lines represent the 95 percent confidence intervals at each time point.

skeletal gain in bone mineral density with parathyroid hormone is lost.

The salutary effects of antiresorptive therapy after treatment with parathyroid hormone are most striking for trabecular bone compartments. At the spine, the two-year cumulative increase was 31 percent among women in whom parathyroid hormone was followed by alendronate, as compared with only 14 percent among women in whom parathyroid hormone was followed by placebo. In addition, we noted positive changes in cortical bone (increases in volume and mineral content but not in density) in the group receiving alendronate after parathyroid hormone that were not seen in the group receiving placebo after parathyroid hormone.

One of the aims of our study was to assess whether two years of combination therapy was superior to two years of monotherapy. Parathyroid hormone followed by alendronate resulted in greater gains in areal bone mineral density than did alendronate alone at sites rich in trabecular bone (e.g., the spine — 12 percent for parathyroid hormone–alendronate therapy vs. 8 percent for continued-alendronate therapy). This was especially evident with regard to volumetric bone mineral density, particularly in the spine, where the parathyroid hormone–alendronate group gained 31 percent, as compared with 6 percent in the continued-alendronate group. However, at sites with more cortical bone, gains with alendronate alone were similar (at the total hip, 4 percent in the parathyroid hormone–alendronate group vs. 3 percent in the continued-alendronate group on dual-energy x-ray absorptiometry) or larger (at the radius). A comparison of the sequential combination with parathyroid hormone alone is more difficult, since our study did not include a group treated with parathyroid hormone alone for two years and, to our knowledge, no study has reported two-year data for parathyroid hormone. However, during 21 months of teriparatide monotherapy, Neer et al.[8] reported gains in bone mineral density similar to those for parathyroid hormone plus alendronate followed by alendronate (9.7 percent at the spine and 2.6 percent at the hip). Thus, from a clinical perspective, one year of parathyroid hormone followed by one year of alendronate would seem to be an effective means of increasing bone mineral density while minimizing the use of parathyroid hormone. However, the effect of this regimen on the risk of fracture is unknown and can be definitively ascertained only in a trial involving fractures.

We also asked whether combination therapy followed by alendronate alone might offer an advantage over other regimens. In the first year, we found no advantage to concurrent combination therapy. Similarly, over two years, gains in areal bone mineral density in the combination-therapy–alendronate group were similar to those in the continued-alendronate group but somewhat lower than those in women who received parathyroid hormone followed by alendronate. Gains in bone mineral density in trabecular bone at the spine were substantially smaller in the combination-therapy–alendronate group (11 percent) than in the parathyroid hormone–alendronate group (31 percent). Taken together, these data do not support the use of alendronate concurrently with parathyroid hormone but suggest that parathyroid hormone alone followed by alendronate alone may be a preferred method of combining these two agents.

Previous reports suggested that antiresorptive therapy after 12 to 21 months of parathyroid hormone therapy — both teriperatide and parathyroid hormone (1–84) — was beneficial in maintaining or increasing areal bone density, but those studies were uncontrolled, observational, and unblinded.[3,5,6,11] It is reassuring that the current findings from the PaTH trial are consistent with the results of those studies, suggesting that our findings are applicable to treatment with both teriparatide and parathyroid hormone (1–84) as well as to varying durations of treatment with parathyroid hormone.

Few previous trials have involved serial measurements of the trabecular and cortical compartments as determined on quantitative CT. Measuring these values may provide insights into how drugs for osteoporosis affect the structure and function of bone. For example, after the cessation of parathyroid hormone therapy, cortical density did not change in either the alendronate or placebo groups over 12 months. However, cortical volume and bone mass increased with alendronate but not with placebo. Increases in cortical volume and mass, with density remaining constant, could improve bone strength and might help explain discrepancies between the relatively small increases in bone density and the larger reductions in the rate of fractures that have been seen with antiresorptive treatments.[12,13] However, to explore more definitively the implications associated with changes in cortical and trabecular bone would require biomechanical modeling,[14] studies in animals, or trials involving fractures in humans.

There are several limitations to this trial. First, it was not large enough to assess the effects of treatment on the rate of fracture, and our conclusions are based on changes in bone mineral density and geometry. However, these changes are remarkably consistent in support of the value of antiresorptive therapy after treatment with parathyroid hormone. The only study of the risk of fracture after parathyroid hormone therapy is a recent 18-month observational, unblinded follow-up after 21 months of teriparatide treatment.[6] This study suggested that teriparatide afforded sustained protection against fracture whether or not antiresorptive therapy was initiated.[6] However, participants self-selected for the use of antiresorptive therapy after parathyroid hormone treatment, making the findings difficult to interpret. Furthermore, one would expect a residual but transient reduction in protection against fracture after treatment with parathyroid hormone without follow-up antiresorptive therapy that might wane over time. Additional studies should address this question. A second limitation is that we cannot be certain that our results are applicable to other types of antiresorptive therapy, including other bisphosphonates. Finally, our study could not address the clinically important question of whether parathyroid hormone can be used successfully after antiresorptive therapy. Some studies (neither randomized nor blinded) have suggested that parathyroid hormone after antiresorptive therapy still has a strong anabolic effect, although the response to parathyroid hormone may be delayed or blunted as a function of the potency and type of antiresorptive therapy.[5,6,15,16]

In summary, increases in bone mineral density during one year of treatment with parathyroid hormone appear to be rapidly lost after therapy is discontinued. Treatment with the bisphosphonate alendronate immediately after the discontinuation of parathyroid hormone either maintains or further increases bone mineral density in year 2. We found no evidence that a concurrent combination of parathyroid hormone and alendronate is superior to either agent alone. Our results are consistent with regard to a wide range of end points involving bone density and bone geometry, suggesting that treatment with parathyroid hormone should be followed by antiresorptive therapy to consolidate the gains made in trabecular and cortical bone density during treatment with parathyroid hormone alone.

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Dr. Black reports having served as a consultant to NPS Pharmaceuticals and Roche and having received lecture fees from Merck and grant support from Merck and Novartis. Dr. Bilezikian reports having received consulting fees from NPS Pharmaceuticals, consulting and lecture fees from Merck, Eli Lilly, and the Alliance for Better Bone Health, and grant support from Eli Lilly and Aventis. Dr. Ensrud reports having received grant support from Pfizer, Eli Lilly, and NPS Pharmaceuticals. Dr. Greenspan reports having received consulting and lecture fees and grant support from Merck and NPS Pharmaceuticals and additional grant support from Novartis and Aventis. Dr. Lang reports having received consulting fees from Amgen and Aventis and lecture fees from Kaiser Permanente, holding stock in GlaxoSmithKline, Pfizer, and Merck, and having received grant support from NPS Pharmaceuticals and Aventis. Dr. Rosen reports having received grant support from Quintiles Canada, Wyeth–Ayerst, Novartis, Merck, Eli Lilly, and Aventis.

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APPENDIX

In addition to the principal investigators, the following persons participated in the PaTH study: *Columbia University* — K. Lee and J. Sliney (study coordinators); *Minneapolis Veterans Affairs Medical Center* — V. Wyum and N. Michaels; *University of Pittsburgh Medical Center* — J.L. Ryan (study coordinator) and J.M. Wagner; *Maine Center for Osteoporosis Research–St. Joseph Hospital* — L. Fowler and D. Storm (study coordinators); *University of California, San Francisco* — T. Hue (project director), L. Palermo (statistician), D. Sellmeyer, and D.C. Bauer (study physicians); *Data Safety Monitoring Board* — L. Raisz, S. Hui, R. Recker, D. Kiel, and D. Hanley.

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ORIGINAL ARTICLE

Daily and Cyclic Parathyroid Hormone in Women Receiving Alendronate

Felicia Cosman, M.D., Jeri Nieves, Ph.D., Marsha Zion, M.S., Lillian Woelfert, R.N., Marjorie Luckey, M.D., and Robert Lindsay, M.D.

ABSTRACT

BACKGROUND

We evaluated whether patients with osteoporosis treated with long-term alendronate have a response to parathyroid hormone treatment and whether short, three-month cycles of parathyroid hormone therapy could be as effective as daily administration.

METHODS

We randomly assigned 126 women with osteoporosis who had been taking alendronate for at least 1 year to continued alendronate plus parathyroid hormone (1–34) subcutaneously daily, continued alendronate plus parathyroid hormone (1–34) subcutaneously daily for three 3-month cycles alternating with 3-month periods without parathyroid hormone, or alendronate alone for 15 months.

RESULTS

In both parathyroid hormone groups, bone formation indexes rose swiftly. Among the women who were receiving cyclic parathyroid hormone, bone formation declined during cycles without parathyroid hormone and increased again during cycles with parathyroid hormone. Bone resorption increased in both parathyroid hormone groups but increased progressively more in the daily-treatment group than in the cyclic-therapy group. Spinal bone mineral density rose 6.1 percent in the daily-treatment group and 5.4 percent in the cyclic-therapy group ($P<0.001$ for each parathyroid hormone group as compared with the alendronate group and no significant difference between parathyroid hormone groups). One woman in the daily-treatment group, two in the cyclic-therapy group, and four in the alendronate group had new or worsening vertebral deformities.

CONCLUSIONS

This study suggests that a regimen of three-month cycles of parathyroid hormone alternating with three-month cycles without parathyroid hormone causes the early phase of action of parathyroid hormone (characterized by pure stimulation of bone formation) to be dissociated from the later phase (activation of bone remodeling). The early phase may be more important to the increase in spinal bone mineral density. In patients with persistent osteoporosis after prior alendronate treatment, both daily treatment and cyclic treatment with parathyroid hormone increase spinal bone mineral density.

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THE USE OF RECOMBINANT HUMAN parathyroid hormone is a novel therapy for osteoporosis with a unique mechanism of action. In contrast to antiresorptive agents, which reduce bone remodeling,[1-5] parathyroid hormone initially stimulates bone formation and later increases bone remodeling.[6] Biochemical indexes of bone formation increase within one month.[7-10] Within six months, indexes of bone resorption are similarly elevated.[7,8] In addition, histomorphometric analyses indicate a dramatic increase in the formation of cancellous bone within four weeks,[11-13] providing evidence that parathyroid hormone stimulates formation without prior resorption. During daily administration of parathyroid hormone, indexes of bone remodeling peak and plateau over a period of 6 to 12 months and then decline.[8,9] The cause of this apparent resistance to continued treatment is unknown. Multiple studies confirm that parathyroid hormone is highly effective at increasing bone mineral density in various populations,[6-9,14-19] with the most rapid increment, consistent with the biochemical data, within the first 6 to 12 months.[6-8] Both the early anabolic window (formation before resorption) and the subsequent resistance to parathyroid hormone suggest that to increase bone mineral density, parathyroid hormone might best be used for periods of 6 to 12 months or less.

Data from several recent studies raise questions about the effectiveness of administering parathyroid hormone with alendronate both in women who have not previously been treated for osteoporosis[20] and in those pretreated with alendronate.[21-23] Patients previously treated with alendronate constitute a large group for whom parathyroid hormone treatment might be indicated, and it is critical to determine whether parathyroid hormone works in these patients.

The objectives of this study were to determine whether parathyroid hormone therapy could improve bone mineral density and biochemical markers of bone turnover in women who had received and were still receiving alendronate and to determine whether short cycles of parathyroid hormone treatment, alternating with periods without parathyroid hormone, which take advantage of the widest window between bone formation and resorption, could produce increments in bone mineral density similar to those induced by daily therapy.

METHODS

SUBJECTS

Volunteers were recruited to Helen Hayes Hospital (West Haverstraw, N.Y.) through our osteoporosis screening center and osteoporosis clinic (1268 women), as well as through local newspaper advertisements and posters (65 women). Twelve potential subjects were identified at the Saint Barnabas Osteoporosis Center (Livingston, N.J.). Of these candidates, 736 were eligible for prescreening to determine their interest in the study and whether they met basic inclusion criteria. After undergoing a prescreening telephone interview, 499 women declined to participate or were ineligible and 209 women attended on-site screening to provide informed consent and undergo a medical interview, physical examination, laboratory evaluation, and measurement of bone mineral density.

Exclusion criteria included rheumatoid arthritis, multiple prior renal stones or a kidney stone within the preceding five years, or current use of glucocorticoids, antiepileptic medications, or estrogen. Subjects were required to have a bone mineral density T score of −2.5 or less at the lumbar spine (two or more vertebrae could be evaluated), femoral neck, or total hip or a T score of −2 or less at any of these sites plus a history of fracture in adulthood (defined as an age of at least 40 years) or vertebral fracture (identified by radiography), but excluding fractures caused by trauma (motor vehicle accidents) and finger, toe, and skull fractures. Normal levels of serum creatinine, total calcium (upper limit, 10.6 mg per deciliter [2.65 mmol per liter]), parathyroid hormone, and thyrotropin; normal liver function and complete blood count; and a ratio of urinary calcium to creatinine of less than 0.35 mg per milligram (1.0 mmol per millimole) after an overnight fast were prerequisites. Subjects with 25-hydroxyvitamin D levels of less than 20 ng per milliliter (50 nmol per liter) received supplements of vitamin D and were enrolled after levels rose to at least 20 ng per milliliter. Seventy-eight women were excluded from the study: 43 did not meet criteria for bone density, fracture, or both; 31 had abnormal laboratory values; and 4 were taking other medications concomitantly. Five women chose not to participate in the study after meeting eligibility criteria.

This study was approved by the institutional review board of Helen Hayes Hospital; all participants

provided written informed consent. A data and safety monitoring board designated by the National Institutes of Health (National Institute of Arthritis, Musculoskeletal, and Skin Diseases) monitored the conduct, safety, and progress of the study. The study began February 24, 2000, and was completed January 7, 2004. Dr. Cosman designed the study, with advice from Drs. Lindsay and Nieves. Drs. Cosman and Lindsay obtained funding. Dr. Cosman and Ms. Woelfert recruited subjects, with help from Drs. Lindsay and Luckey. Dr. Cosman and Ms. Woelfert were responsible for patient care and supervision of data collection, and Dr. Lindsay monitored safety and outcome data. Ms. Zion performed all primary data analyses with advice from Dr. Nieves, and they both vouch for the integrity of the data and analyses. Dr. Cosman wrote the manuscript with help from Drs. Lindsay, Nieves, and Luckey and Ms. Zion. There were no pharmaceutical sponsors, and the influence of the sponsor, the National Institute of Arthritis, Musculoskeletal, and Skin Diseases, was limited to the data and safety monitoring board.

Baseline Measurements

Baseline serum samples were obtained from the women the morning after an overnight fast. Serum levels of intact parathyroid hormone were measured by an iodine-125 radioimmunoassay (Nichols Institute). Serum levels of 25-hydroxyvitamin D were measured by an iodine-125 radioimmunoassay (Diasorin). Indexes of bone formation were determined as follows: bone-specific alkaline phosphatase was measured by enzyme immunoassay (Quidel), osteocalcin was measured by an immunoradiometric assay (Immutopics), and N-terminal propeptide of type I procollagen was measured by an Osteomark enzyme-linked immunosorbent assay (Ostex International). Baseline second-void fasting urine samples were analyzed for bone resorption by measuring the levels of cross-linked urinary N-telopeptide with the use of an enzyme-linked immunosorbent assay (Ostex International) and creatinine. Serum and urinary calcium and urinary creatinine were assayed by standard automated methods. All intraassay coefficients of variation were less than 8.3 percent, and interassay coefficients of variation were less than 13.7 percent.

Baseline bone mineral density at the spine, at the hip, and of the total body was measured with the use of the Lunar Prodigy (General Electric/Lunar). In vivo the short-term precision of this approach was 0.7 percent for spinal measurements and 0.9 percent for total-hip measurements; the long-term precision (two years) of this approach was lower than 1.7 percent for all sites. Lateral thoracic and lumbar spine radiographs were obtained at baseline for the determination of the prevalence of vertebral fractures.

Treatment

Subjects were randomly assigned by a computer, in blocks of 18, to receive 70 mg of alendronate weekly (43 women), daily parathyroid hormone plus alendronate (43 women), or cyclic parathyroid hormone plus alendronate (40 women) for 15 months. Daily parathyroid hormone was administered subcutaneously as synthetic human parathyroid hormone (1–34) in a daily dose of 25 μg. Cyclic parathyroid hormone was administered in the same fashion at the same dose, except that each treatment cycle lasted three months and was followed by three months without parathyroid hormone. Calcium intake was assessed by means of a food-frequency questionnaire, and all subjects maintained their total calcium intake (with supplements given when necessary) between 1200 and 1500 mg per day. Vitamin D supplementation was provided to achieve levels of 25-hydroxyvitamin D of more than 20 ng per milliliter. There were no placebo injections. Both the study nurse and the physician were aware of a woman's treatment-group assignment but were unaware of study outcomes. Those responsible for outcome measurements were unaware of the women's treatment assignments.

Parathyroid hormone was synthesized by Bachem, inserted into vials by Bionebraska/Restoragen, and tested for bioactivity with the use of the chick hypercalcemia assay (TNO Bibra International). Subjects self-injected parathyroid hormone, rotating sites, with 56 percent of the women using both the abdomen and thighs, 30 percent using solely the thighs, and 14 percent using solely the abdomen. Most subjects administered the medication in the morning, though two administered it in the evening. There were no significant differences in the changes in bone mineral density at the lumbar spine among women injecting parathyroid hormone primarily into their thigh, women who used primarily abdominal sites, and women who used both sites.

Follow-up Measurements

Fasting morning blood samples and second-void urine samples were obtained approximately 24

hours after the last injection. Efficacy biochemical analyses (bone formation and resorption variables), selected safety biochemical analyses (serum calcium and ratio of urinary calcium to creatinine), and measurements of bone mineral density at the spine and hip were performed every three months. Additional safety biochemical analyses (creatinine levels, liver-function tests, and a complete blood count) were performed at 12 months with the use of standard automated techniques. Measurement of bone mineral density of the total body and lateral thoracolumbar radiography were repeated at 15 months.

Determination of Vertebral Fractures

Spine radiographs were digitized by BioImaging Technologies. Points were placed on end plates of T4 to L5, and height ratios were calculated.[24-26] Prevalent fractures were defined by ratios 3 or more SD below the mean of a reference population.[27] Incident vertebral fractures (new or worsening) were defined by a decrease of at least 20 percent in one of the heights by morphometric assessment,[28,29] if also confirmed by semiquantitative review by two investigators, who were unaware of the results of quantitative analyses. One subject was found to have an incidental vertebral fracture by semiquantitative review alone. Radiographs were reviewed in chronologic sequence, with treatment-group assignment and patient identifiers removed.

Statistical Analysis

The preplanned primary hypothesis was that both parathyroid hormone regimens would induce an increase in spinal bone mineral density as compared with alendronate alone and that the magnitude of this increment would be similar in the two groups. The study had a statistical power of 90 percent to detect an absolute difference of 3 percent in the spinal bone mineral density increment between the two parathyroid hormone groups, given the enrollment of 33 women in each group, and greater statistical power to identify differences in either parathyroid hormone group as compared with the alendronate group. Analyses were based on the 108 women who completed the 15-month protocol, since 56 percent of withdrawals occurred before the three-month visit. Analyses based on the intention to treat did not differ significantly from those based on treatment actually received.

Data were evaluated for normality and log-transformed where necessary. Baseline differences were evaluated by means of analysis of variance for continuous variables and the chi-square test for categorical variables. A mixed-model analysis of variance was used to assess the primary hypothesis of the effect of treatment on bone mineral density. Bone mineral density was analyzed as the percent change from baseline. To assess whether the primary unadjusted hypothesis test was robust with

Table 1. Characteristics of the Women.*

Characteristic	Daily Parathyroid Hormone + Alendronate (N=43)	Cyclic Parathyroid Hormone + Alendronate (N=40)	Alendronate Only (N=43)
Age — yr	67.1±7.6	67.4±8.0	70.7±7.1
Years from menopause	19.5±10.6	20.7±8.7	22.1±8.9
Height — in.	63.2±3.5	62.8±3.6	62.2±2.6
Weight — lb	139.2±25.7	130.9±22.0	136.3±22.4
Spine			
Bone mineral density — g/cm²	0.838±0.11	0.847±0.08	0.833±0.10
T score	−2.9±0.9	−2.8±0.8	−2.9±0.8
Total hip			
Bone mineral density — g/cm²	0.761±0.11	0.739±0.09	0.768±0.01
T score	−2.0±0.9	−2.1±0.7	−1.9±0.8
Prior nonspinal fracture in adulthood — no. (%)	26 (60)	23 (58)	13 (30)†
Prevalent vertebral fractures — no. (%)	22 (51)	18 (45)	21 (49)
Years of alendronate therapy	2.8±0.2	3.5±0.3	3.0±1.0

* Plus–minus values are means ±SD. To convert height to centimeters, divide by 0.3937. To convert weight to kilograms divide by 2.2.

† P<0.001 for the comparison with the parathyroid hormone groups.

respect to potential confounders, including age, years from menopause, weight, height, body-mass index (defined as the weight in kilograms divided by the square of the height in meters), years of prior alendronate therapy, and presence or absence of a history of fracture, these variables were assessed in separate models. Biochemical variables were analyzed by repeated-measures analysis of variance. Exact logistic regression, controlling for the presence or absence of fracture in adulthood, was used to evaluate whether the number of new or worsening vertebral fractures differed among the three groups. All analyses were two-sided, with an alpha value of 0.05.

RESULTS

BASELINE CHARACTERISTICS

Baseline characteristics are shown in Table 1. The mean (±SD) age of the women was 68.4±7.6 years. Overall, 48 percent of the women had vertebral compression deformities at baseline (no significant differences among the groups). The only significant baseline difference among the groups was in the number of prior nonspinal clinical fractures during adulthood. However, if fractures of the feet, toes, fingers, and ankles were excluded, there were no significant differences among the groups. Baseline biochemical data (Table 2) were similar across groups, except for the mean ratio of urinary calcium to creatinine, which was slightly higher in the group given daily parathyroid hormone (P<0.001). Mean bone turnover levels were all in the low normal range, with no significant group differences.

WITHDRAWALS

Eighteen subjects withdrew from the study: five women in the group given daily parathyroid hormone, six in the group given cyclic parathyroid hormone, and seven in the alendronate group. Fifty-six percent of withdrawals occurred during the first three months of the study. Reasons for withdrawal are shown in Table 3.

ADHERENCE

Adherence to parathyroid hormone therapy was assessed by reviewing the women's diaries and counting the number of empty parathyroid hormone vials that were returned, and alendronate adherence was assessed by interviewing the women. Adherence to all treatment regimens exceeded 90 percent. Of the 108 women who completed the study, 99 percent completed 100 percent of study visits.

BIOCHEMICAL EFFICACY VARIABLES

There were no significant biochemical changes in the alendronate group during the study (Fig. 1). In the group given daily parathyroid hormone, markers of bone formation rose from 116 percent in the case of bone-specific alkaline phosphatase to 373 percent in the case of N-terminal propeptide of

Table 2. Baseline Biochemical Characteristics of the Women.*

Variable	Daily Parathyroid Hormone + Alendronate (N=43)	Cyclic Parathyroid Hormone + Alendronate (N=40)	Alendronate Only (N=43)
Serum			
Calcium (mg/ml)	9.3±0.3	9.3±0.4	9.3±0.3
Parathyroid hormone (1–84) (pg/ml)	34.8±16.3	37.5±16.5	40.1±14.6
25-Hydroxyvitamin D (ng/ml)	25.9±6.5	25.0±8.3	24.6±8.9
Bone-specific alkaline phosphatase (U/liter)	12.8±3.7	13.2±3.9	13.0±5.4
Osteocalcin (ng/ml)†	5.2±1.7	5.2±1.8	4.8±1.7
N-propeptide of type 1 procollagen (μg/liter)	22.9±13.8	22.1±13.2	19.9±12.9
Urine			
Calcium:creatinine ratio‡	0.22±0.1	0.15±0.1	0.13±0.1
N-telopeptide:creatinine ratio	29.0±16.2	27.9±14.9	25.4±14.0

* Plus–minus values are means ±SD.
† To convert values for osteocalcin to nanomoles per liter, multiply by 0.1724.
‡ Both calcium and creatinine were measured in milligrams. P<0.001 for the comparison of the daily-therapy group with the other two groups.

type I procollagen above baseline values. The bone-resorption marker cross-linked urinary N-telopeptide rose more slowly and to a lesser extent (93 percent above baseline values). Among the women who were receiving cyclic parathyroid hormone, markers increased similarly during the first three months of therapy and declined during the periods without parathyroid hormone therapy. During the second and third cycles of parathyroid hormone therapy, markers of bone formation rose to a similar degree as seen during the first cycle. Levels of urinary N-telopeptide did not rise to as great an extent as in the daily-therapy group during the second and third cycles of parathyroid hormone; in fact, there was a progressive separation in urinary N-telopeptide values between the daily-therapy and cyclic-therapy groups during the 15 months.

BONE DENSITY

At 15 months, bone mineral density at the lumbar spine (Fig. 2) had not changed significantly from baseline values in the alendronate group but increased 6.1 percent in the group given daily parathyroid hormone and 5.4 percent in the group given cyclic parathyroid hormone ($P<0.001$). This increase did not differ significantly between the parathyroid hormone groups. Adjustment for covariates did not alter the significance of the effects of parathyroid hormone on bone mineral density. Eighty-five percent of women in the parathyroid hormone groups had an increase in spinal bone mineral density: 72 percent had an increase of at least 3 percent, 58 percent had an increase of at least 5 percent, 14 percent had an increase of at least 10 percent, and 6 percent had an increase of at least 15 percent. There was no relationship between the duration of prior alendronate use and the change in either spinal bone mineral density or biochemical markers. Baseline biochemical markers correlated weakly with changes in spinal bone mineral density ($r=0.26$ for osteocalcin, $r=0.25$ for bone-specific alkaline phosphatase, $r=0.38$ for N-terminal propeptide of type I procollagen, and $r=0.37$ for cross-linked urinary N-telopeptide; all $P<0.05$). In the parathyroid hormone groups, an increase of more than 30 percent in any of the biochemical markers at 3 months had a posi-

Table 3. Withdrawals and Adverse Events.

Event	Daily Parathyroid Hormone + Alendronate (N=43)	Cyclic Parathyroid Hormone + Alendronate (N=40)	Alendronate (N=43)
Reasons for withdrawal — no. (%) of randomized women			
Multiple nonspecific symptoms	5 (12)	5 (12)	2 (5)
Randomly assigned to alendronate alone group	0	0	2 (5)
New diagnosis of breast cancer	0	0	1 (2)
New diagnosis of rheumatoid arthritis	0	1 (2)	0
Death from complications of aortic-valve surgery	0	0	1 (2)
Practical or transportation issues	0	0	1 (2)
Total withdrawals	5 (12)	6 (15)	7 (16)
Adverse events — no. (%) of women who completed study			
Musculoskeletal symptoms*	10 (26)	4 (12)	2 (6)
Redness at injection site*	1 (3)	6 (18)	0
Gastrointestinal effects	9 (24)	7 (21)	4 (11)
Generalized fatigue	2 (5)	3 (9)	0
Cardiac symptoms	5 (13)	3 (9)	3 (8)
Vascular symptoms	2 (5)	1 (3)	0
Elevated total serum calcium	1 (3)	1 (3)	0
Elevated urinary calcium:creatinine ratio*	15 (39)	6 (18)	3 (8)
Elevated serum creatinine	0	0	0
Elevated liver-function tests	1 (3)	0	2 (6)
Abnormal complete blood count	5 (13)	4 (12)	2 (6)

* $P<0.05$ for the difference among the groups.

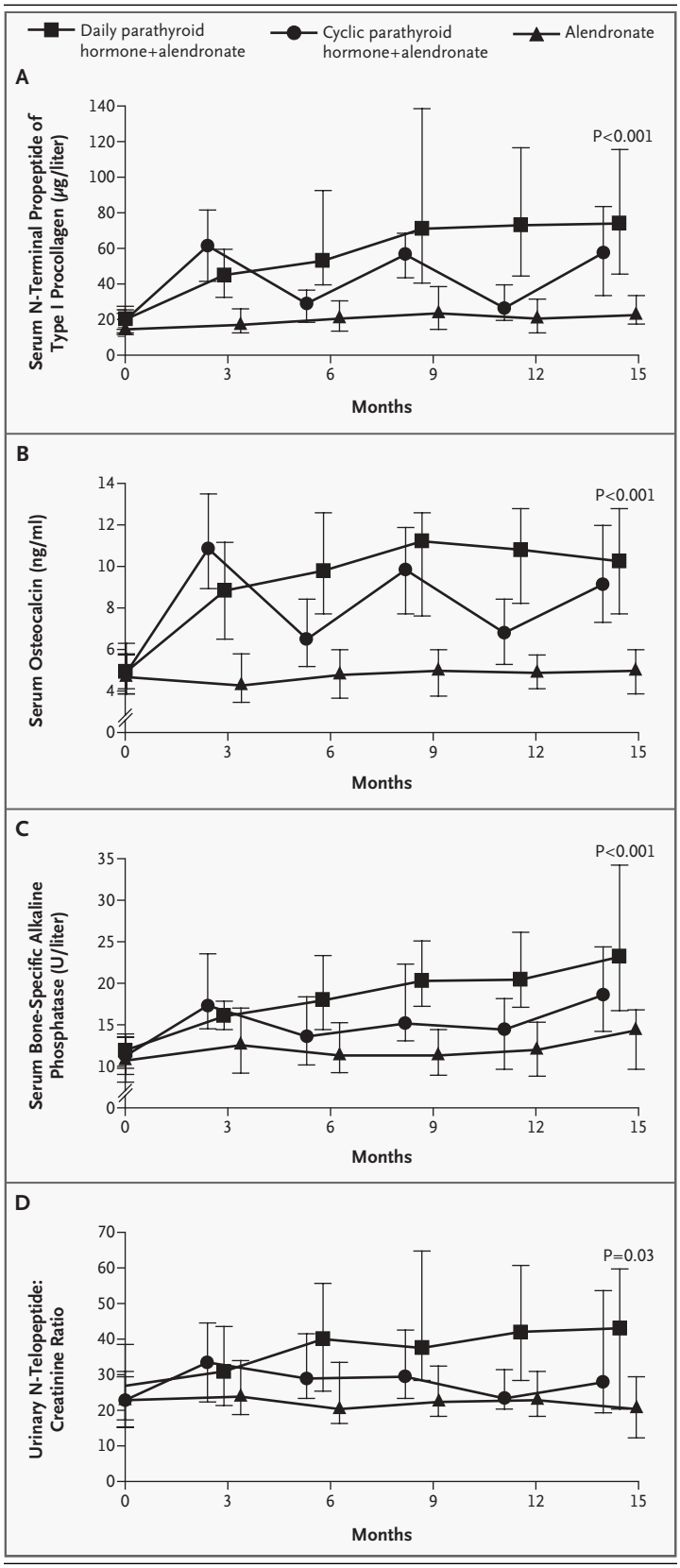

Figure 1. Median Changes in Indexes of Bone Formation (Panels A, B, and C) and Resorption (Panel D) among the Group Given Daily Parathyroid Hormone plus Alendronate, the Group Given Cyclic Parathyroid Hormone plus Alendronate, and the Group Given Alendronate Alone.

I bars denote the interquartile range. P values are for the time–treatment interactions among the three groups. To convert values for osteocalcin to nanomoles per liter, multiply by 0.1724.

tive predictive value of more than 73 percent for an increase in spinal bone mineral density of at least 3 percent at 15 months.

Bone mineral density at the hip (Fig. 2) increased slightly in all three groups (P<0.05), with no significant differences among the groups. There were no significant changes in total-body bone mineral density in any of the three groups (data not shown).

INCIDENCE OF FRACTURES

New or worsening vertebral deformities occurred in 1 of 38 women in the group given daily parathyroid hormone (3 percent), 2 of 34 women in the group given cyclic parathyroid hormone (6 percent), and 4 of 36 women in the alendronate group (11 percent; P=0.20 for the difference among the groups). Clinical nonspinal fractures occurred in four women in the group given daily parathyroid hormone (calcaneus, toe and wrist, shoulder, and metatarsal), two in the group given cyclic parathyroid hormone (hip and elbow), and two in the alendronate group (two ribs and metatarsal).

SAFETY

Adverse events are reported in Table 3. One woman in each parathyroid hormone group had minimally elevated serum calcium levels during early treatment, and these levels returned to normal spontaneously by the next preplanned sampling one week later. All but 1 of 24 women with elevated ratios of urinary calcium to creatinine had a spontaneous return to normal values by the next sampling; the value normalized in this woman after the dose of her calcium supplement was decreased (according to the planned algorithm). None of the women required a reduction in the dose of medication.

DISCUSSION

Our data suggest that, after prior and continuing treatment with alendronate, the administration of parathyroid hormone stimulates bone formation

and enhances spinal bone mass. Many women with osteoporosis, previously treated with bisphosphonates, might benefit from parathyroid hormone therapy because of the possibility of intercurrent fractures, active bone loss, persistently low bone mineral density, or an inability to tolerate ongoing bisphosphonate treatment. Whether the response to parathyroid hormone in these patients is identical to the response in patients who have never received treatment cannot be ascertained on the basis of the available data and is not clinically relevant for patients who have been previously treated with alendronate. Although small and not statistically powered to evaluate fracture outcomes, our study suggests that parathyroid hormone may further reduce the incidence of vertebral deformity in patients who have previously been treated with alendronate; this possibility needs to be confirmed in a larger trial.

The bone density findings in our study differ somewhat from those in an observational study of women who were given parathyroid hormone daily for 18 months after discontinuing alendronate or raloxifene therapy.[23] The baseline biochemical markers were lower in the alendronate group in that study than in ours, particularly for bone-specific alkaline phosphatase and cross-linked urinary N-telopeptide, and the baseline turnover may predict the bone mineral density response. However, the magnitude of change in remodeling biochemical variables with parathyroid hormone therapy was similar in the two studies.

In the other study, an initial slight decline in bone mineral density at the hip was seen in the group that had previously received alendronate, whereas our study showed no evidence of a loss of bone mineral density at the hip, perhaps because alendronate was continued during parathyroid hormone treatment. The discontinuation of alendronate, even after long-term treatment, results in a decline in the bone mineral density at the hip.[30] Stimulation of bone turnover by parathyroid hormone may further accelerate this loss after the withdrawal of alendronate. However, ultimately (after six months of parathyroid hormone treatment), bone mineral density at the hip returned to baseline values in that investigation.[23] A randomized trial to evaluate the effect of continuation or discontinuation of alendronate would be required to determine whether this is the cause of the difference in the change in bone mineral density at the hip between the studies. The changes we observed in spinal bone mineral density were greater (6.1 percent vs. 4.2 percent), despite our use of a slightly shorter treatment period (15 vs. 18 months). This may relate to our use of a slightly higher dose of parathyroid hormone (25 μg per day vs. 20 μg per day), since the change in bone mineral density is dose dependent.[6]

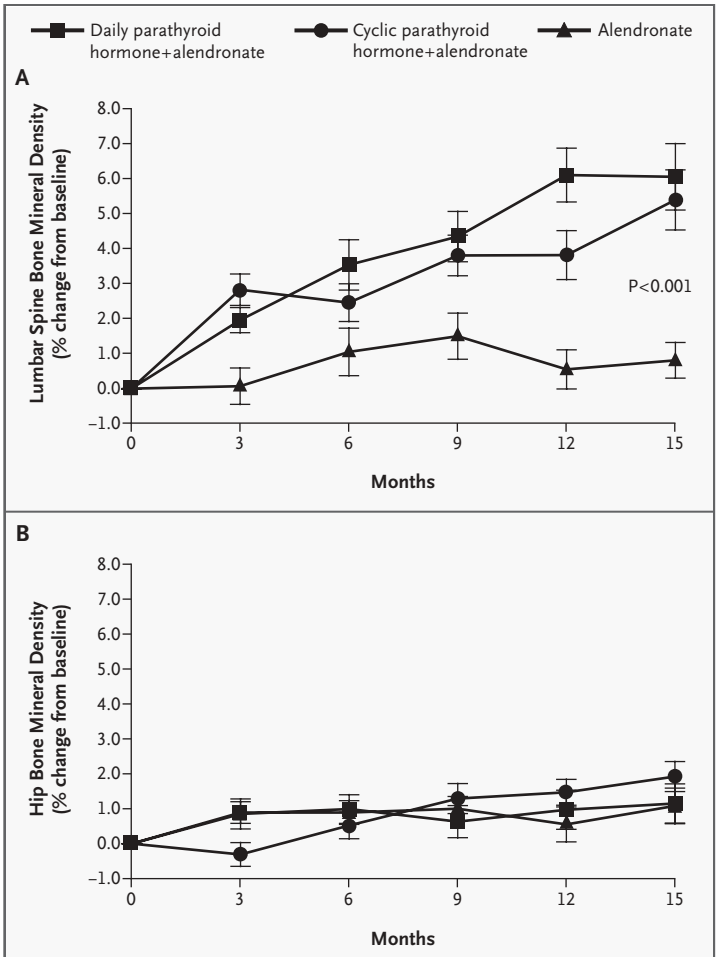

Figure 2. Mean Changes in Bone Mineral Density at the Lumbar Spine (Panel A) and the Total Hip (Panel B) among the Group Given Daily Parathyroid Hormone plus Alendronate, the Group Given Cyclic Parathyroid Hormone plus Alendronate, and the Group Given Alendronate Alone.

In Panel A, P<0.001 for the overall time–treatment interaction for the three groups. There was no significant difference in the time–treatment interaction between the cyclic-therapy and daily-treatment groups. In Panel B, all three groups had small, significant increases in bone mineral density at 15 months, as compared with baseline values, but the percent change did not differ significantly among the groups. I bars denote the SEs.

Our study does not address the distinct clinical issue of concomitant treatment with parathyroid hormone and alendronate in patients who have never been treated for osteoporosis. Several recent investigations[20-22] indicate that in such patients,

administering parathyroid hormone with alendronate or providing a short course of alendronate treatment before parathyroid hormone therapy does not further augment the increase in spinal bone mineral density. The parathyroid hormone used in one of these studies[20] was a different molecule, the full, intact peptide, parathyroid hormone (1–84). Biochemical results in the group given parathyroid hormone plus alendronate in that study suggest that osteoblast activity is stimulated initially (within the first month), but then inhibition of bone resorption becomes the dominant effect, and when new remodeling sites are no longer initiated under the influence of alendronate, the rate of bone formation declines. Differences in the response of the osteogenic unit (committed precursors, mature bone cells, and their microenvironment) to simultaneous treatment with the two agents, as compared with sequential therapy, are likely to account for unique responses to parathyroid hormone administration in patients who have never received treatment, as compared with patients who have already received alendronate.

The concept of cyclic administration of parathyroid hormone was based on the hypothesis that early direct stimulation of bone formation by parathyroid hormone might be more important to the ultimate accrual of bone mineral density than later activation of bone remodeling by parathyroid hormone. The short cycle of parathyroid hormone largely dissociates the early anabolic effect from the latter remodeling-based effects of parathyroid hormone. The fact that the increase in bone mineral density at the spine was similar with cyclic and daily therapy, after only 60 percent of the daily dose had been given, suggests that this, indeed, might be true, at least for spinal bone mineral density. Furthermore, the biochemical data from the cyclic-therapy group confirm that a second course of parathyroid hormone can stimulate bone formation with a magnitude similar to that induced by the first course of parathyroid hormone after a short interval without therapy. Further study is warranted to determine whether short cycles of parathyroid hormone for a more extended period would be superior to a single two-year course of therapy.

Our data confirm that parathyroid hormone can exert a biologically meaningful increase in bone mineral density and should be considered for patients who have previously received alendronate (and perhaps other bisphosphonates) who are still at high risk for fracture. The main end points of our study — bone turnover and bone density — reflect some, but not all, of the mechanisms (macroarchitecture and microarchitecture) underlying the parathyroid hormone–mediated increase in bone strength. The parathyroid hormone–induced increment in spinal bone mineral density may be slightly lower in women who have previously received alendronate than in women who have never received alendronate; however, the magnitude of the change in spinal bone mineral density is still impressive. Our data suggest that intermittent cyclic treatment with parathyroid hormone produces effects on bone mineral density similar to those induced by daily administration, but at a lower cost and with less effort on the part of patients. Use of the change in bone mineral density induced by the combination of these medications to predict the effect on fractures should be performed with caution and only after a fracture trial has been conducted.

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ORIGINAL ARTICLE

Developmental Outcomes after Early or Delayed Insertion of Tympanostomy Tubes

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ABSTRACT

BACKGROUND

To prevent later developmental impairments, myringotomy with the insertion of tympanostomy tubes has often been undertaken in young children who have persistent otitis media with effusion. We previously reported that prompt as compared with delayed insertion of tympanostomy tubes in children with persistent effusion who were younger than three years of age did not result in improved developmental outcomes at three or four years of age. However, the effect on the outcomes of school-age children is unknown.

METHODS

We enrolled 6350 healthy infants younger than 62 days of age and evaluated them regularly for middle-ear effusion. Before three years of age, 429 children with persistent middle-ear effusion were randomly assigned to have tympanostomy tubes inserted either promptly or up to nine months later if effusion persisted. We assessed developmental outcomes in 395 of these children at six years of age.

RESULTS

At six years of age, 85 percent of children in the early-treatment group and 41 percent in the delayed-treatment group had received tympanostomy tubes. There were no significant differences in mean (±SD) scores favoring early versus delayed treatment on any of 30 measures, including the Wechsler Full-Scale Intelligence Quotient (98±13 vs. 98±14); Number of Different Words test, a measure of word diversity (183±36 vs. 175±36); Percentage of Consonants Correct–Revised test, a measure of speech-sound production (96±2 vs. 96±3); the SCAN test, a measure of central auditory processing (95±15 vs. 96±14); and several measures of behavior and emotion.

CONCLUSIONS

In otherwise healthy children younger than three years of age who have persistent middle-ear effusion within the duration of effusion that we studied, prompt insertion of tympanostomy tubes does not improve developmental outcomes at six years of age.

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Among children in the United States, otitis media is the most commonly diagnosed illness after the common cold,[1] and myringotomy with the insertion of tympanostomy tubes is the most common operation beyond the newborn period.[2] An estimated 280,000 children younger than three years of age underwent the operation in 1996 (Kozak LJ: personal communication). Often the operation has been undertaken in young children to relieve persistent middle-ear effusion, out of concern that the commonly associated conductive hearing loss might have lasting adverse effects on the cognitive, speech, language, or psychosocial development of the children.[3-5] Supporting that practice have been official guidelines recommending the operation for otherwise healthy children in whom middle-ear effusion has persisted for as long as three months[6] or four months.[3]

In 1991, because of the limited and inconclusive evidence concerning the relation between otitis media during a child's early years and his or her later development[7-10] and because of the lack of evidence that the insertion of tympanostomy tubes favorably affected the development of children with persistent middle-ear effusion, we began a study to address these issues. Previously, we reported that among study participants younger than three years of age who had persistent effusion for the periods defined later in this article, early insertion of tympanostomy tubes, as compared with delayed insertion, did not result in improved developmental outcomes at three or four years of age.[11-13] This report describes developmental findings in these children at six years of age, when the findings are expected to be more predictive of the functioning of these children in later life.

METHODS

GENERAL PROCEDURES

The study included two main components. One was a randomized clinical trial in which children with persistent middle-ear effusion were assigned to undergo either prompt insertion of tympanostomy tubes or delayed insertion if effusion persisted. The other component consisted of a representative subgroup of children not meeting the randomization criteria and examined the relation between the cumulative duration of middle-ear effusion and the later developmental outcomes of the children. We have described the study procedures in detail previously.[11,14,15] In brief, from June 1991 through December 1995 we enrolled 6350 healthy infants who were 2 to 61 days of age at the following eight sites: Children's Hospital of Pittsburgh, Mercy Hospital of Pittsburgh, and two small-town and rural and four suburban private pediatric group practices in the Pittsburgh area. The study was approved by the institutional review boards of the two hospitals. Written informed consent was obtained from one or both parents or the guardians of each enrolled infant.

We monitored children's middle-ear status at least monthly from the time of enrollment until three years of age. We used the term "middle-ear effusion" to encompass all types of otitis media in which effusion was present; we estimated the cumulative proportions of days that each child had unilateral effusion or bilateral effusion on the basis of diagnoses made at individual visits and interpolations for intervals between visits; and we conducted audiometric testing frequently when effusion was present. Since most testing was conducted with the use of speakers rather than earphones, results reflected function mainly in the better-hearing ear. We found hearing to be abnormal in approximately half the children with unilateral effusion and approximately three quarters of those with bilateral effusion.[11]

RANDOMIZED CLINICAL TRIAL

Children became eligible for the clinical trial if, from 61 days of age to 3 years of age, they had middle-ear effusion that appeared substantial in degree and that persisted, despite antimicrobial treatment, for 90 days in the case of bilateral effusion or 135 days in the case of unilateral effusion. Children with intermittent effusion for specified proportions of longer periods were also eligible, according to the criteria listed previously.[11] For example, a child was eligible if he or she had had bilateral effusion for at least 67 percent of the preceding 180-day period or unilateral effusion for at least 67 percent of the preceding 270-day period. Children who met one of these criteria and whose parents or guardians gave written consent were stratified according to practice site, age (in six-month categories), and whether they met the eligibility criteria on the basis of bilateral or unilateral effusion. They were then assigned randomly, within those strata and in balanced blocks of four children, to undergo insertion of tympanostomy tubes either promptly (the early-treatment group) or six months later if bilateral effusion persisted or nine months later if unilateral effusion persisted (the delayed-treatment group).

After consent had been obtained, designated nonclinical staff members made assignments with the use of separate, computer-generated lists of random numbers. Children assigned to the delayed-treatment group were able to receive tube insertion earlier if their parents requested the operation. Children for whom consent for randomization was withheld were offered tube insertion electively. Regardless of whether they underwent the surgery, they were then monitored less frequently but were scheduled for the same developmental testing procedures as those planned for the children who underwent randomization.

As anticipated, children in the early-treatment group had substantially less middle-ear effusion after randomization than children in the delayed-treatment group. For example, during the first 12 months after randomization, 45 percent of the children in the delayed-treatment group had middle-ear effusion for more than 50 percent of the days, as compared with 14 percent of the children in the early-treatment group.[11]

REPRESENTATIVE SUBGROUP

We randomly selected the comparison sample to represent the demographics of the study population as a whole and to represent a spectrum of children ranging from those with no middle-ear effusion to those just short of meeting the criteria for randomization. In these children, the estimated cumulative duration of effusion (unilateral and bilateral combined) ranged from no middle-ear effusion to 66 percent of their first year of life and to 45 percent of their first three years of life.[15]

DEVELOPMENTAL TESTS AND PROCEDURES

We assessed the cognitive, language, speech, and psychosocial development of the children with the use of formal tests, conversational samples, and parental questionnaires. We attempted to conduct assessments of the children as soon as possible after their sixth birthday, at times when hearing-level thresholds were 15 dB or less in each ear at 1000, 2000, and 4000 Hz. We used the following measures: the Wechsler Intelligence Scale for Children, third edition,[16] for intelligence; the Peabody Picture Vocabulary Test–Revised, Form M,[17] for receptive vocabulary; the SCAN test[18] for disorders of auditory processing of language; the Nonword Repetition Task[19] for phonologic memory; the Number of Different Words test[20,21] for vocabulary diversity; the Mean Length of Utterance in Morphemes test[21-23] for sentence length and grammatical complexity; the Percentage of Consonants Correct–Revised[21,24] for speech sound production; the Parenting Stress Index, Short Form,[25] for parent–child stress; and the parent and teacher versions of the Child Behavior Checklist[26] for behavior.

Details about test conditions, examiners, and procedures and the recording, transcription, and analysis of conversational samples have been described previously.[13,15,21] The examiners, transcriptionists, and analysts were blinded to the health histories (including receipt of tympanostomy tubes) and health insurance status of the children and the level of education of the mothers. Randomly selected samples of language constituting at least 10 percent of the total were subjected to second, independent transcription and analysis; interobserver reliability ranged from 91 to 94 percent.

STATISTICAL ANALYSIS

We calculated the duration of middle-ear effusion in children beginning when they were 61 days of age. In the clinical trial, we assumed a priori that a difference of at least 0.33 SD on any outcome measure favoring the early-treatment group would be clinically important. For the study to have the ability to detect such differences at a power of 0.80, we calculated that 182 children would be needed in each group. Results of the trial were based on the intention-to-treat principle.

In the representative subgroup, the original sample size of 241 children was sufficient to detect correlations of 0.20, at a power of 0.71, between children's scores on developmental tests and their estimated cumulative proportions of days with middle-ear effusion, and correlations of 0.25 at a power of 0.91. Because correlations involving days with bilateral effusion differed little from correlations involving days with any effusion (i.e., bilateral or unilateral), all analyses presented here concern total days with any effusion.

We used two-tailed tests for all analyses and set statistical significance at $P \leq 0.05$. We used chi-square tests to evaluate differences in proportions among children in different groups. We used analysis of variance to test for differences between mean values, pairwise Pearson correlation analysis to test for correlations, and linear regression analysis to adjust for potentially confounding variables and to test for interactions.

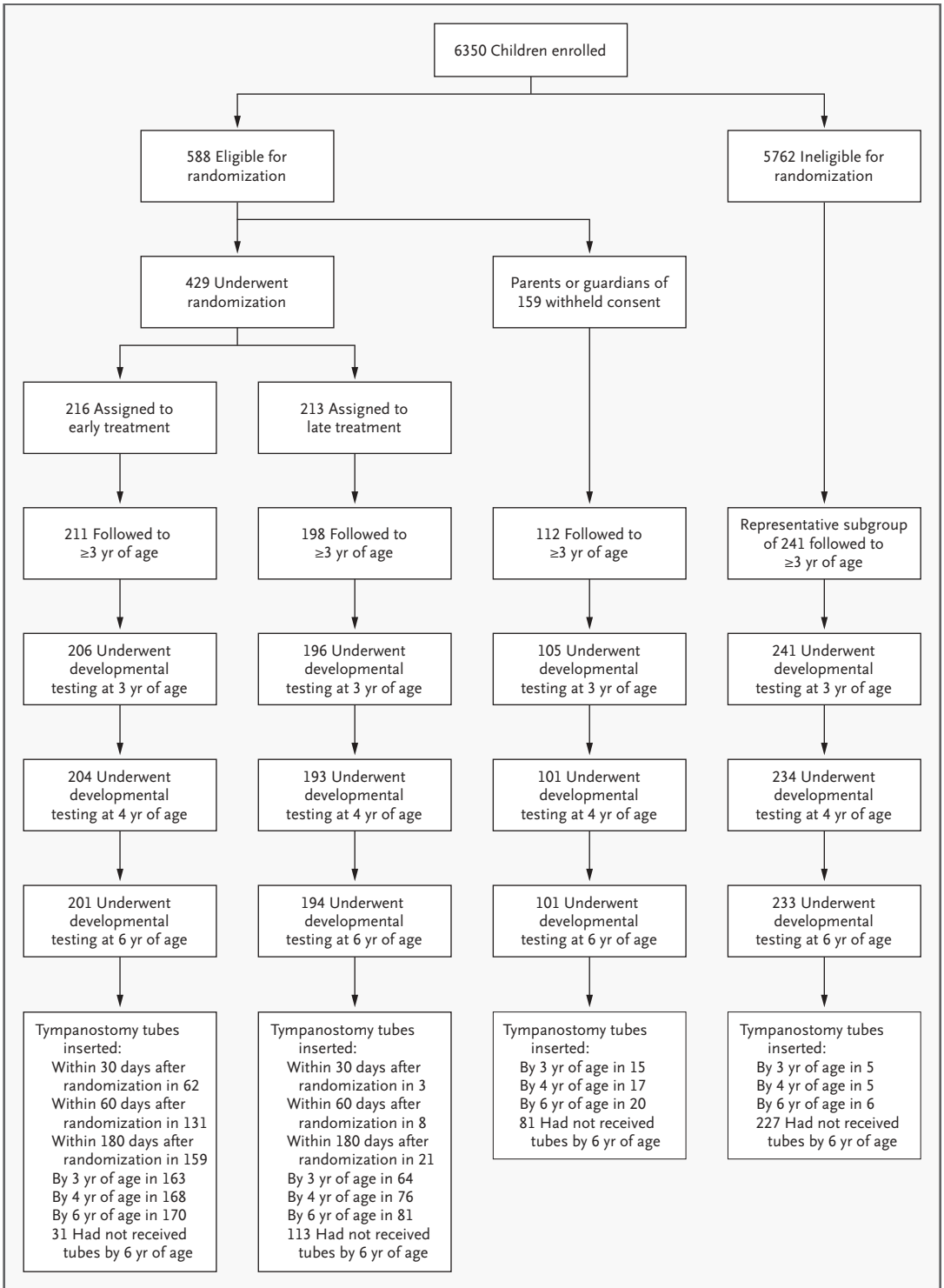

Figure 1. Enrollment, Randomization, and Follow-up of the Children and the Time of Insertion of Tympanostomy Tubes.
Two of the children who underwent developmental testing at six years of age — one in the early-treatment group of the clinical trial and one in the delayed-treatment group — were not tested at either three or four years of age.

RESULTS

STUDY SAMPLE AND TREATMENT GROUPS

Of 6350 children enrolled in the study, 588 eventually met the eligibility criteria for the clinical trial; of these, 429 children (73 percent) underwent randomization after their parents or guardians gave consent. A total of 395 (92 percent) of the children who underwent randomization, 101 of the 159 children (64 percent) whose parents or guardians declined randomization, and 233 of the 241 children (97 percent) in the representative subgroup underwent developmental testing at six years of age (Fig. 1).

Table 1 shows selected demographic characteristics of the children who were tested. In the clinical trial, there were no significant differences in characteristics between the tested children in the early-treatment and delayed-treatment groups, or between the 395 children who were tested and the 34 children who were not. Table 2 shows pertinent clinical characteristics of the children who underwent randomization; there were no significant differences between groups. In 684 of the 729 children tested (94 percent), testing was completed within two months after their sixth birthday. The mean scores of the participants in the study on all developmental measures are shown in Table 3.

CLINICAL TRIAL

There were no significant differences between the early-treatment and the delayed-treatment groups, except for a moderately higher score among the children in the delayed-treatment group on the Nonword Repetition Task (76±10 vs. 74±10, $P<0.05$). Results were materially unchanged after adjustment for the age in months when testing occurred and, in the case of measures of language samples, for

Table 1. Demographic Characteristics of the Children Who Underwent Testing, According to Study Component.*

Characteristic	Randomized Clinical Trial (N=395)	Group for Whom Consent for Randomization Was Withheld (N=101)	Representative Subgroup (N=233)
		no. of children (%)	
Location of study site			
Urban	192 (49)	69 (68)†	58 (25)†
Small town or rural	143 (36)	17 (17)	88 (38)
Suburban	60 (15)	15 (15)	87 (37)
Sex			
Male	225 (57)	55 (54)	117 (50)
Female	170 (43)	46 (46)	116 (50)
Race or ethnic group‡			
Black	143 (36)	52 (51)§	38 (16)†
White	241 (61)	45 (45)	192 (82)
Other or indeterminate	11 (3)	4 (4)	3 (1)
Maternal level of education			
Less than high school	52 (13)	20 (20)	22 (9)†
High-school graduate	310 (78)	71 (70)	162 (70)
College graduate	33 (8)	10 (10)	49 (21)
Health insurance status			
Medicaid	252 (64)	73 (72)	75 (32)†
Private	140 (35)	27 (27)	154 (66)
None	3 (1)	1 (1)	4 (2)

* Because of rounding, percentages may not sum to 100.
† $P<0.001$ for the comparison with the distribution of children who underwent randomization.
‡ Race or ethnic group was assigned by the interviewer.
§ $P<0.01$ for the comparison with the distribution of children who underwent randomization.

Table 2. Clinical Characteristics of the Tested Children Who Underwent Randomization.*

Characteristic	Early-Treatment Group (N=201)	Delayed-Treatment Group (N=194)
	no. of children (%)	
Year of life during which randomization criteria were met		
First	81 (40)	78 (40)
Second	92 (46)	94 (48)
Third	28 (14)	22 (11)
Laterality and sequence of middle-ear effusion serving as the basis for meeting randomization criteria		
Bilateral, continuous	40 (20)	33 (17)
Bilateral, discontinuous	38 (19)	34 (18)
Unilateral, continuous	33 (16)	30 (15)
Unilateral, discontinuous	90 (45)	97 (50)
Hearing test abnormal on ≥1 occasion before randomization†		
Yes	164 (82)	140 (72)
No	22 (11)	32 (16)
Results incomplete or unreliable, or children not tested	15 (7)	22 (11)
Percent of time with bilateral middle-ear effusion in the 6-month period before meeting randomization criteria‡		
≤25	30 (15)	40 (21)
26–50	79 (39)	67 (35)
51–75	77 (38)	76 (39)
76–99	12 (6)	8 (4)
100	3 (1)	3 (2)
Percent of time with bilateral middle-ear effusion in the 6-month period before meeting randomization criteria, in the subgroup of children meeting the criteria on the basis of unilateral effusion‡§		
≤25	30 (24)	39 (31)
26–50	57 (46)	53 (42)
51–75	35 (29)	32 (25)
76–99	1 (1)	3 (2)
100	0	0
Hearing thresholds at time of developmental testing at 6 yr of age		
Protocol-specified criteria met¶	180 (90)	181 (93)
Protocol-specified criteria not met	19 (9)	11 (6)
Audiometric results incomplete or child's hearing not tested	2 (1)	2 (1)
Middle-ear effusion status at time of developmental testing at 6 yr of age		
None	177 (88)	170 (88)
Unilateral	15 (7)	20 (10)
Bilateral	7 (3)	3 (2)
Indeterminate	2 (1)	1 (<1)

* There were no significant differences in characteristics between the two treatment groups. Because of rounding, percentages may not sum to 100.
† On the basis of data obtained from children in the study who had no effusion,[27] abnormal hearing tests were defined as an auditory brainstem–response threshold >20 dB hearing level (HL) or a pure-tone average >25 dB HL up to the age of 10 months, >20 dB HL from 10 to 23 months, and >15 dB HL from the age of 2 years onward.
‡ For the 63 children (29 in the early-treatment group and 34 in the delayed-treatment group) who met the criteria before 9 months of age, the period extended from 61 days of age (the starting point for data analysis) to the date the criteria were met.
§ There were 123 children in the early-treatment group and 127 in the delayed-treatment group.
¶ The criteria consisted of a hearing-level threshold of ≤15 dB at 1000, 2000, and 4000 Hz.

Table 3. Scores on Developmental Tests at Six Years of Age.*

Test	Randomized Clinical Trial (N=395)			Group for Whom Consent for Randomization Was Withheld (N=101)	Representative Subgroup (N=233)
	Early-Treatment Group (N=201)	Delayed-Treatment Group (N=194)	95% CI†		
	mean score (no. of children)			*mean score (no. of children)*	
Formal tests‡					
Wechsler Intelligence Scale for Children					
Full-scale IQ	98±13 (199)	98±14 (194)	−3.0 to 2.5	97±14 (101)	105±14 (233)
Verbal IQ	98±13 (199)	98±14 (194)	−2.8 to 2.6	97±13 (101)	104±14 (233)
Performance IQ	98±14 (201)	99±15 (194)	−3.2 to 2.5	97±15 (101)	105±15 (233)
Peabody Picture Vocabulary Test	94±14 (200)	94±20 (193)	−3.6 to 3.2	93±16 (100)	104±15 (233)
SCAN test	95±15 (178)	96±14 (177)	−4.6 to 1.5	96±14 (96)	100±15 (231)
Nonword Repetition Task	74±10 (182)	76±10 (176)§	−4.1 to 0.1	74±11 (97)	79±11 (216)
Conversational samples‡					
Number of Different Words	183±36 (188)	175±36 (186)	0.0 to 14.4	177±43 (98)	180±36 (225)
Mean Length of Utterance in Morphemes	3.9±0.8 (188)	3.8±0.7 (186)	−0.1 to 0.2	3.9±0.8 (98)	3.9±0.7 (225)
Percentage of Consonants Correct	96±2 (188)	96±3 (185)	−0.5 to 0.4	96±2 (98)	96±2 (226)
Parent-reported inventories¶					
Parenting Stress Index, Short Form					
Parental Stress subscale	22±7 (194)	23±8 (189)	−2.1 to 1.0	21±7 (94)	21±7 (231)
Parent–Child Dysfunctional Interaction subscale	19±6 (194)	19±7 (189)	−1.5 to 1.2	18±6 (94)	17±6 (231)
Difficult Child subscale	25±8 (194)	25±9 (189)	−1.5 to 1.9	24±7 (94)	23±7 (231)
Total Stress score	66±19 (194)	66±22 (189)	−4.5 to 3.7	63±18 (94)	62±17 (231)
Child Behavior Checklist					
Withdrawn scale	53±5 (197)	52±5 (193)	−0.8 to 1.0	52±4 (93)	52±4 (229)
Somatic Complaints scale	53±5 (197)	53±5 (193)	−1.5 to 0.4	53±5 (93)	53±5 (229)
Anxious/Depressed scale	52±5 (197)	52±3 (193)	−0.3 to 1.3	52±4 (93)	52±5 (229)
Social Problems scale	53±6 (197)	53±5 (193)	−0.2 to 2.0	53±5 (93)	52±4 (229)
Thought Problems scale	53±6 (197)	53±6 (193)	−1.2 to 1.1	54±6 (93)	52±4 (229)
Attention Problems scale	54±6 (197)	54±6 (193)	−1.3 to 1.0	54±6 (93)	52±4 (229)
Delinquent Behavior scale	54±6 (197)	54±6 (193)	−1.2 to 1.2	54±5 (93)	53±4 (229)
Aggressive Behavior scale	55±7 (197)	54±7 (193)	−1.1 to 1.7	54±6 (93)	53±5 (229)
Total Problems score	49±11 (197)	48±11 (193)	−1.5 to 2.7	48±10 (93)	46±10 (229)

the total numbers of words and of utterances in the sample. There were no significant interactions to suggest that outcomes differed in relation to whether children met the randomization criteria of the study during their first, second, or third year of life; whether they met the criteria on the basis of bilateral continuous middle-ear effusion, unilateral continuous effusion, bilateral discontinuous effusion, or unilateral discontinuous effusion; and, in the 358 children who received hearing tests during one or more episodes of effusion before undergoing randomization, whether one or more of those tests gave abnormal results (as defined in Table 2) or showed a pure-tone average threshold of 30 dB or more or 40 dB or more. (Thresholds of 31 to 50 dB constitute moderate hearing loss.[28])

Among the children who underwent randomization, mean scores for those who actually received tympanostomy tubes before three years of age (irrespective of treatment assignment) as com-

Table 3. (Continued.)

Test	Randomized Clinical Trial (N=395)			Group for Whom Consent for Randomization Was Withheld (N=101)	Representative Subgroup (N=233)
	Early-Treatment Group (N=201)	Delayed-Treatment Group (N=194)	95% CI†		
Teacher-reported inventory¶					
Child Behavior Checklist					
Withdrawn scale	53±6 (192)	54±7 (186)	−1.7 to 1.0	53±6 (93)	52±5 (222)
Somatic Complaints scale	52±4 (192)	52±5 (186)	−1.3 to 0.5	51±4 (93)	52±4 (222)
Anxious/Depressed scale	52±4 (192)	53±5 (186)	−1.7 to 0.3	52±4 (93)	53±4 (222)
Social Problems scale	54±5 (192)	53±6 (186)	−0.8 to 1.4	53±5 (93)	52±4 (222)
Thought Problems scale	52±6 (192)	52±6 (186)	−0.9 to 1.4	53±6 (93)	51±4 (222)
Attention Problems scale	56±8 (192)	55±8 (186)	−0.8 to 2.3	55±8 (93)	53±5 (222)
Delinquent Behavior scale	54±6 (192)	53±5 (186)	−0.4 to 1.9	54±7 (93)	52±4 (222)
Aggressive Behavior scale	55±8 (192)	54±7 (186)	−1.0 to 2.0	55±9 (93)	53±5 (222)
Total Problems score	49±11 (192)	48±11 (186)	−1.2 to 3.3	49±11 (93)	46±10 (222)

* Plus–minus values are means ±SD.
† The 95 percent confidence interval (CI) is for the difference in mean scores (early-treatment group minus delayed-treatment group).
‡ Higher scores indicate more favorable results. In the Wechsler Intelligence Scale for Children, third edition,[16] the number of correct responses is calculated. The normative mean verbal IQ, performance IQ, and full-scale IQ are each 100±15. In the Peabody Picture Vocabulary Test–Revised,[17] the number of correct responses is calculated. The normative mean score is 100±15. For the SCAN Screening Test for Auditory Processing Disorders[18] to be completed successfully, the hearing level has to be normal. A composite score is calculated from the number of correctly understood distorted words, speech in the presence of background noise, and different words presented simultaneously to the two ears. The normative mean score is 100±15. In the Nonword Repetition Task,[19] in standardized phonologic strings of increasing length (one, two, three, and four syllables) in nonsense words, the percentage of phonemes repeated correctly is calculated. Values shown are limited to children with values for all four lengths of strings. In the Number of Different Words test,[20,21] from a computer-assisted analysis of the transcribed sample, all first-occurrence word roots, ignoring inflectional morphemes, are counted in all utterances. In the Mean Length of Utterance in Morphemes test,[21-23] from a computer-assisted analysis of the transcribed sample, the mean length of all utterances that were both complete and intelligible is calculated. In the Percentage of Consonants Correct–Revised test,[21,24] from a computer-assisted analysis of the phonetically transcribed sample, the first 100 first-occurrence words in the transcript are analyzed for the percentage of intended consonants that are articulated correctly. Speech-sound substitutions and omissions are scored as incorrect and speech-sound distortions as correct.
§ $P<0.05$ for the comparison with the early-treatment group.
¶ Higher scores indicate less favorable results. In the Parenting Stress Index, Short Form,[25] the parent rates the parent–child dyad on 36 items in three subscales in terms of the degree of agreement with each statement ("strongly agree," "agree," "not sure," "disagree," or "strongly disagree"). The total of the scores on the subscales is the total stress score. The normative mean scores are 26±7 for the Parental Stress subscale; 19±5 for the Parent–Child Dysfunctional Interaction subscale; 26±7 for the Difficult Child subscale; and 71±15 for the Total Stress score. For the Child Behavior Checklist,[26] a parent and a teacher independently rate the overall behavioral and emotional problems of the child by responding to 120 items and scoring each statement as "not true," "somewhat or sometimes true," or "very or often true." The results are organized into eight specific scales. Scores on the eight scales and a Total Problems score are calculated and converted to T scores. The normative mean T score on each scale and for Total Problems is 50±10.

pared with mean scores for those who did not showed only one significant difference: the mean score on the Nonword Repetition Task was higher among the children who had not received tubes (76±10 vs. 74±11, P=0.04). There were no significant differences between the mean scores of children who underwent randomization and those of children for whom randomization was declined or, in the latter group, between the mean scores of children who received tympanostomy tubes and those who did not.

REPRESENTATIVE SUBGROUP

In the representative subgroup, unadjusted correlations between the scores on each outcome measure and the cumulative duration of middle-ear effusion in the children during their first, second, and third years of life and during their first two years and first three years of life were all less than 0.25; most were less than 0.10 and most were nonsignificant. Exceptions consisted of significant negative correlations (range, −0.13 to −0.18) between the percentage of days with effusion during one or more of

those age periods and scores on the Peabody Picture Vocabulary Test–Revised and the Mean Length of Utterance in Morphemes test, and significant positive correlations (range, 0.13 to 0.22) between percentages of days with effusion and scores on all subscales of the Parenting Stress Index, Short Form, and on certain scales of the parent and teacher versions of the Child Behavior Checklist.

Because scores on most measures were most favorable among the most socioeconomically advantaged children (as indicated by the location of the study site, maternal level of education, and health insurance status) and scores on measures of language and speech were significantly higher in girls than in boys, we performed analyses adjusting for these variables and for hearing thresholds at the time of testing (categorized as within or above protocol-specified limits). Most of the correlations that were significant in unadjusted analyses remained significant (data not shown). However, the percent of the variance in scores explained by time with middle-ear effusion beyond that explained by demographic variables was low, ranging from 1.8 to 4.9 percent.

DISCUSSION

The present findings in children who had persistent middle-ear effusion during their first three years of life indicate that prompt insertion of tympanostomy tubes had no demonstrable beneficial effect on their developmental outcomes at six years of age. These findings reinforce our findings in the study participants at three and four years of age and extend those findings to include results of measures newly applied at six years of age. These measures consisted of a test for deficits in central auditory processing, considered by some authors to constitute the underlying basis of many learning problems[29] and by others to be caused by persistent early-life otitis media[30]; a formal test of intelligence; and teachers' ratings of the behavior of the children.

Other authors have observed that measures of intellectual function[31] and measures of language[32] become increasingly predictive of later IQ as age increases from two to approximately six years, after which predictability levels off, and that both IQ and parents' and teachers' reports of behavior during school-age years correlate with later academic performance.[33,34] Therefore, it seems likely that the results we obtained in the children at six years of age will correlate with the functioning of the children later. To determine whether developmental effects not discernible by 6 years of age might become apparent later, we are currently testing the children at 9 to 11 years of age with the use of measures of literacy, attention, and related skills.

On all of the 30 measures we applied, we found no significant differences in scores favoring the early-treatment group over the delayed-treatment group in the clinical trial. For 26 of the measures, the associated 95 percent confidence intervals afforded assurance that the presence of any difference of 0.33 SD or larger favoring the early-treatment group would probably have been detected. In children in the representative subgroup, correlations between the cumulative duration of middle-ear effusion in the first three years of life and developmental outcomes were, as we had found at earlier ages,[13,15,35] generally weak and in most instances nonsignificant. For the few significant associations found, the percent of variance in the results explained by time with effusion beyond that explained by demographic variables was negligible. The findings in the clinical trial suggest that these associations reflect chance, residual confounding, or both.

Citing our findings in children who underwent randomization at three years of age,[11,12] a clinical practice guideline recently issued by representatives of the American Academy of Family Physicians, the American Academy of Otolaryngology–Head and Neck Surgery, and the American Academy of Pediatrics recommends that otherwise healthy children with persistent otitis media with effusion, instead of undergoing tube insertion, "should be reexamined at 3- to 6-month intervals until the effusion is no longer present, significant hearing loss is identified, or structural abnormalities of the eardrum or middle ear are suspected."[36] Our findings support the recommendation not to insert tubes simply on the basis of persistent effusion and seem generally applicable to children in primary care settings in whom middle-ear effusion is an isolated condition.

As we have noted previously,[11,13] these findings cannot be generalized to children who are not otherwise healthy or who have handicapping conditions such as sensorineural hearing loss, cleft palate, or Down's syndrome, or to children with periods of effusion longer than those we studied, or to children whose effusion is consistently accompanied by moderately severe (rather than the more usual

mild-to-moderate) hearing loss. However, both clinical experience and our previously reported findings[13] suggest that relatively few children in circumstances similar to those of the children in our trial will have periods of effusion substantially longer than those of the participants in the trial.

In summary, our findings in children who were six years of age, consistent with our results when they were three and four years of age, show that the insertion of tympanostomy tubes for persistent otitis media with effusion in the first three years of life, within the duration of effusion that we studied, does not improve the developmental outcomes of the children at those ages. These data, together with the risks posed by the insertion of tubes,[37-40] provide clear support for managing the treatment of such children conservatively.

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ORIGINAL ARTICLE

Rocky Mountain Spotted Fever from an Unexpected Tick Vector in Arizona

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ABSTRACT

BACKGROUND

Rocky Mountain spotted fever is a life-threatening, tick-borne disease caused by *Rickettsia rickettsii*. This disease is rarely reported in Arizona, and the principal vectors, *Dermacentor* species ticks, are uncommon in the state. From 2002 through 2004, a focus of Rocky Mountain spotted fever was investigated in rural eastern Arizona.

METHODS

We obtained blood and tissue specimens from patients with suspected Rocky Mountain spotted fever and ticks from patients' homesites. Serologic, molecular, immunohistochemical, and culture assays were performed to identify the causative agent. On the basis of specific laboratory criteria, patients were classified as having confirmed or probable Rocky Mountain spotted fever infection.

RESULTS

A total of 16 patients with Rocky Mountain spotted fever infection (11 with confirmed and 5 with probable infection) were identified. Of these patients, 13 (81 percent) were children 12 years of age or younger, 15 (94 percent) were hospitalized, and 2 (12 percent) died. Dense populations of *Rhipicephalus sanguineus* ticks were found on dogs and in the yards of patients' homesites. All patients with confirmed Rocky Mountain spotted fever had contact with tick-infested dogs, and four had a reported history of tick bite preceding the illness. *R. rickettsii* DNA was detected in nonengorged *R. sanguineus* ticks collected at one home, and *R. rickettsii* isolates were cultured from these ticks.

CONCLUSIONS

This investigation documents the presence of Rocky Mountain spotted fever in eastern Arizona, with common brown dog ticks (*R. sanguineus*) implicated as a vector of *R. rickettsii*. The broad distribution of this common tick raises concern about its potential to transmit *R. rickettsii* in other settings.

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ROCKY MOUNTAIN SPOTTED FEVER, which is caused by *Rickettsia rickettsii*, is a life-threatening, tick-borne disease that occurs throughout much of the United States. Case fatality rates can be as high as 20 percent in untreated patients.[1,2] The principal recognized vectors of *R. rickettsii* are *Dermacentor variabilis* (the American dog tick) (Fig. 1A) in the eastern and central United States and *D. andersoni* (the Rocky Mountain wood tick) (Fig. 1B) in the western United States. Both types of tick feed on small mammals, which may harbor *R. rickettsii*. *D. variabilis*, the most common tick associated with Rocky Mountain spotted fever, also commonly feeds on dogs.[3] Another common tick throughout the world that feeds on dogs, *Rhipicephalus sanguineus* (the brown dog tick) (Fig. 1C), has not previously been reported to be a natural vector for Rocky Mountain spotted fever in the United States.

Rocky Mountain spotted fever is rarely reported in Arizona, and the expected *Dermacentor* species vectors are not commonly found in the state.[4] From 1981 through 2001, only three cases of Rocky Mountain spotted fever were reported for the entire state.[1,2] However, from 2002 through 2004, Rocky Mountain spotted fever was identified in 16 patients from rural eastern Arizona. In this report, we describe that outbreak and summarize the clinical, epidemiologic, and ecologic findings that implicate *R. sanguineus* as a newly recognized vector for *R. rickettsii* in the region.

METHODS

LABORATORY TESTING

Serum, whole-blood, or tissue specimens for diagnostic testing were obtained from patients in whom Rocky Mountain spotted fever was suspected because they had a fever of 38°C (100.5°F) or higher, a maculopapular rash, or both. Serum samples were tested with the use of indirect immunofluorescence assays for IgG and IgM antibodies reactive with *R. rickettsii*; the assays were performed at commercial laboratories and at the Centers for Disease Control and Prevention (CDC) in Atlanta.[5] Tissue specimens were evaluated at the CDC with the use of an immunohistochemical stain to detect the spotted-fever–group rickettsiae.[6] DNA was extracted from whole blood, serum sediment, or tissue with the use of a commercial kit (QIAamp DNA Mini Kit, Qiagen) and assayed in a nested polymerase-chain-reaction (PCR) assay at the CDC to amplify a fragment of the 17-kD antigen gene (*htrA*) of the spotted-fever–group rickettsiae.[7] Samples that were positive on this assay were further tested with the use of a PCR assay targeting a portion of the *rOmpA* gene, and species identification of *R. rickettsii* was confirmed through direct DNA sequencing or restriction-fragment–length polymorphism analysis of the amplified products.[8,9] A confirmed case of Rocky Mountain spotted fever was defined as one in which there was at least one of the following findings: a change by a factor of four or more in the antibody titer between paired serum specimens; a skin-biopsy or autopsy-tissue specimen that was positive on immunohistochemical staining for spotted-fever–group rickettsiae; *R. rickettsii* DNA-positive serum, whole blood, or tissue; and isolation in culture on Vero E6 cells of *R. rickettsii* from patient samples.[10,11] A probable case of Rocky Mountain spotted fever was defined as one in which there was a reciprocal IgM or IgG antibody titer of 64 or more in a single serum sample or in paired samples that did not show a change by a factor of four or more in antibody titer.

CASE INVESTIGATIONS

From 2003 through 2004, patients with Rocky Mountain spotted fever were identified through active surveillance at the regional hospital serving the affected communities. Reviews of medical charts provided information about these patients. Interviews with patients and family members assessed possible tick exposures, descriptions of the home environment, and contact with dogs. Patients in whom the onset of illness occurred before 2003 were identified through anecdotal reports and their cases documented through the retrospective review of medical charts.

INVESTIGATION OF DOGS AND TICKS FROM PATIENTS' HOMESITES

Serum samples were obtained from dogs owned by patients and tested with the use of an immunofluorescence assay for IgG antibodies reactive to *R. rickettsii*. Ticks were collected from patient homesites with the use of dry ice as an attractant, hand picking from various substrates, and flannel flags dragged over vegetation and bare ground during September 2003, June 2004, and September 2004. All ticks were identified with the use of standard taxonomic keys. Quantitative PCR[12] and DNA sequencing were

used to detect *R. rickettsii* DNA in ticks, as described above. A subgroup of ticks were homogenized and inoculated onto Vero E6 cells.[10,11] *R. rickettsii*–positive cultures were confirmed with the use of PCR and DNA sequencing.

RESULTS

EPIDEMIOLOGIC AND CLINICAL CASE FINDINGS

During the period from June 2002 through October 2004, 11 confirmed and 5 probable Rocky Mountain spotted fever infections were identified in a 6700-km² (2600 square-mile) region of rural eastern Arizona. Ten patients (62 percent) were male, and 13 (81 percent) were 12 years of age or younger (median age, 7.5 years; range, 9 months to 68 years) (Table 1). Seven patients resided in a single small community (population, approximately 2148) in this circumscribed region. Nine additional patients resided in a second community (population, approximately 10,000) located about 50 miles away. None of the patients or their families reported having traveled outside the region in the two weeks before the onset of illness. The average annual incidence (from 2002 through 2004) of Rocky Mountain spotted fever among children and adolescents 19 years of age or younger in the region was 1800 cases per million persons.

Laboratory, epidemiologic, and clinical features of the 16 patients with confirmed or probable Rocky Mountain spotted fever are presented in Table 1. Cases were confirmed through one or more of the following methods: the detection of spotted-fever–group rickettsiae in skin-biopsy or tissue specimens on immunohistochemical staining (five patients) (Fig. 2), seroconversion (eight patients), or PCR amplification of *R. rickettsii* DNA in serum, blood, skin, or lung tissue (four patients). *R. rickettsii* isolates were cultured from tissue specimens from two patients.

All patients had contact with tick-infested dogs. Four patients (25 percent) had a known history of tick bite, and a *R. sanguineus* nymph was found attached to Patient 3. Fifteen patients (94 percent) had fever of 38°C (100.5°F) or higher, and 15 (94 percent) had maculopapular rashes, of which 13 involved the palms or soles during the course of illness. Other reported signs and symptoms included cough or sore throat (five patients), nausea or vomiting (five), myalgia (four), diarrhea (three), ab-

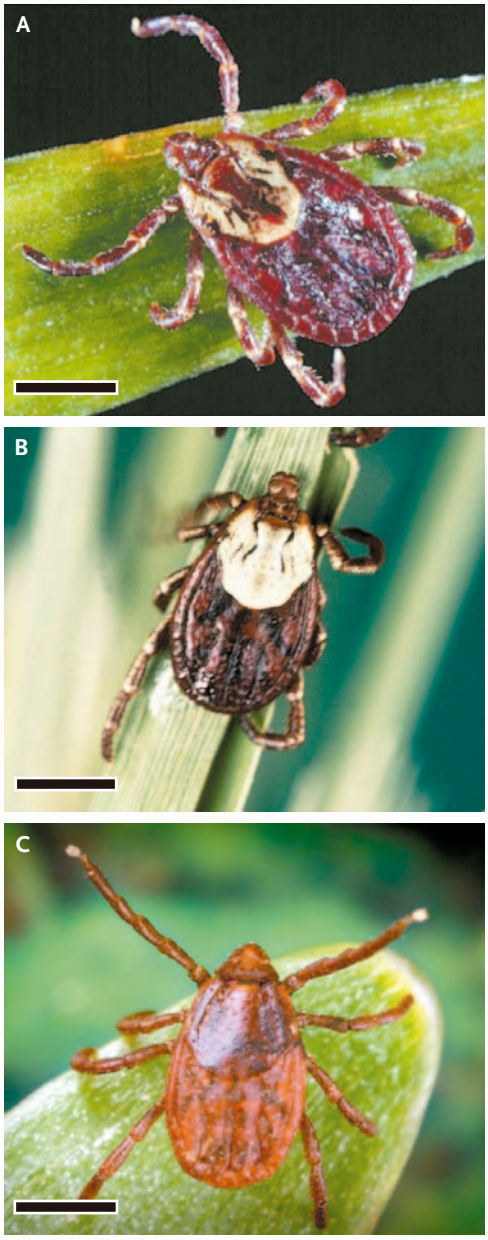

Figure 1. The Principal Recognized Tick Vectors of *Rickettsia rickettsii*.

Panel A shows *Dermacentor variabilis,* or the American dog tick, Panel B *D. andersoni,* or the Rocky Mountain wood tick, and Panel C *Rhipicephalus sanguineus,* or the brown dog tick. The scale bar in each image represents 2 mm. All ticks shown are adult females, which represent the largest developmental stage; males, nymphs, and larvae are progressively smaller. *R. rickettsii* may be transmitted by ticks at all stages of development.

Table 1. Characteristics of Patients with Confirmed or Probable Rocky Mountain Spotted Fever Infections in Arizona, 2002 through 2004.*

Patient No.	Date of Illness Onset	Age	Sex	Maculopapular Rash	Fever ≥38°C (100.5°F)	History of Tick Bite	Outcome	Laboratory Diagnostic-Test Results	Case Classification
1	June 4, 2002	10 yr	Male	+	+	+	Recovered	Paired serum samples: 4-fold change in IgG titer	Confirmed
2	Aug. 13, 2003	14 mo	Male	+	+	–	Died	PCR of serum sample	Confirmed
3	May 21, 2004	10 yr	Male	+	+	+	Recovered	IHC of skin-biopsy specimen; paired serum samples: 4-fold change in IgG titer	Confirmed
4	May 22, 2004	19 mo	Male	+	+	–	Recovered	IHC of skin-biopsy specimen; PCR of whole blood; paired serum samples: 4-fold change in IgG titer	Confirmed
5	June 13, 2004	22 yr	Male	+	–	–	Recovered	Single serum sample, IgM ≥1024	Probable
6	June 14, 2004	3 yr	Male	+	+	–	Recovered	IHC of skin-biopsy specimen; paired serum samples: 4-fold change in IgG titer	Confirmed
7	July 23, 2004	5 yr	Female	–	+	–	Died	PCR of whole blood and lung tissue; IHC of biopsy specimen from multiple organs; tissue-culture isolate	Confirmed
8	Aug. 1, 2004	8 yr	Female	+	+	–	Recovered	Paired serum samples: both IgM=256	Probable
9	Aug. 9, 2004	25 yr	Male	+	+	–	Recovered	Paired serum samples: 4-fold change in IgG titer	Confirmed
10	Aug. 15, 2004	8 yr	Male	+	+	–	Recovered	Paired serum samples: both IgM=256	Probable
11	Sept. 6, 2004	6 yr	Female	+	+	–	Recovered	Paired serum samples: 4-fold change in IgM titer	Confirmed
12	Sept. 9, 2004	68 yr	Female	+	+	+	Recovered	PCR of skin-biopsy specimen; tissue-culture isolate	Confirmed
13	Sept. 20, 2004	12 yr	Female	+	+	+	Recovered	IHC of skin-biopsy specimen; paired serum samples: 4-fold change in IgM titer	Confirmed
14	Sept. 20, 2004	9 mo	Male	+	+	–	Recovered	Paired serum samples: 4-fold change in IgG titer	Confirmed
15	Sept. 25, 2004	7 yr	Male	+	+	–	Recovered	Paired serum samples: IgM=256, IgM= 512	Probable
16	Nov. 9, 2004	17 mo	Female	+	+	–	Recovered	Paired serum samples: IgM=64, IgM=128	Probable

* PCR denotes polymerase-chain-reaction assay, and IHC immunohistochemical staining. Plus signs indicate the presence of a finding, and minus signs its absence.

dominal pain (two), and headache (two). Common laboratory findings included elevated hepatic aminotransferase levels (aspartate aminotransferase, >36 U per liter; alanine aminotransferase, >52 U per liter; nine patients), hyponatremia (serum sodium, <130 mmol per liter; eight patients), and thrombocytopenia (platelet count, <130,000 per cubic millimeter; four patients). Fifteen patients (94 percent) required hospitalization, and six (38 percent) required treatment in an intensive care unit. Patients 2 and 7, in whom Rocky Mountain spotted fever was not initially suspected and in whom treatment with doxycycline was not started or was initiated late in the clinical course of illness, died from the infection. The overall case fatality rate, calculated over three years, was 12 percent.

In addition to the 16 cases presented here, we retrospectively identified 3 additional patients from the same communities in whom illness began during 2001 and whom we suspected had Rocky Mountain spotted fever. All three patients had an illness clinically compatible with a diagnosis of Rocky

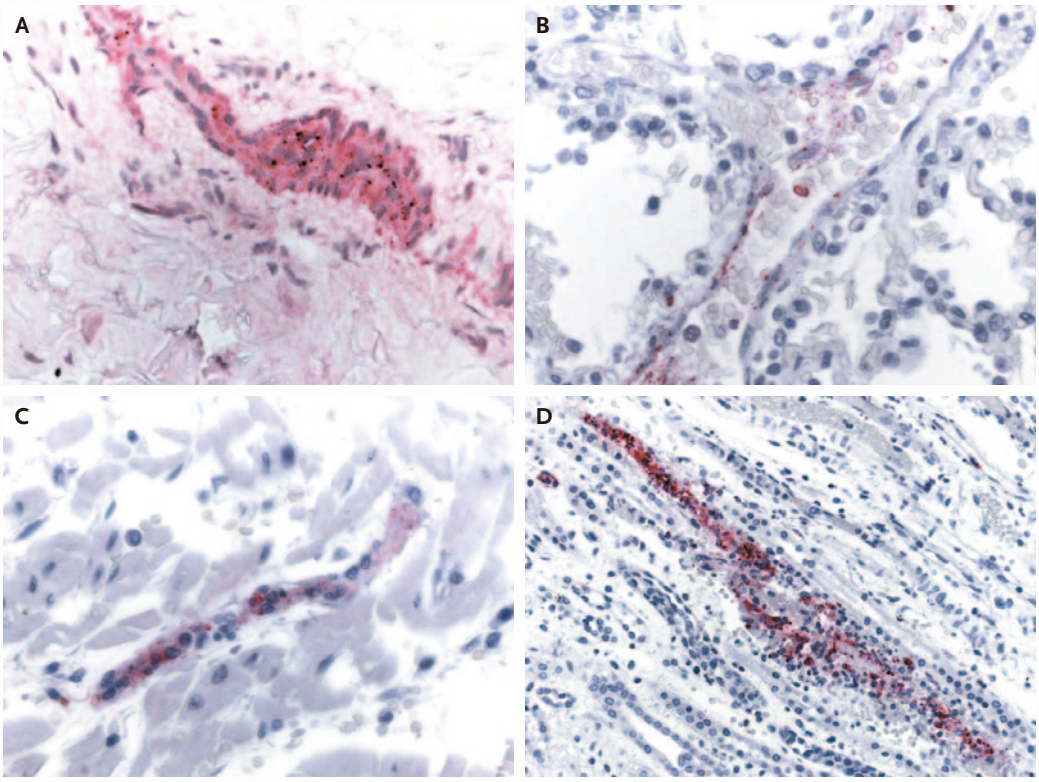

Figure 2. Immunohistochemical Staining of Skin-Biopsy and Autopsy Specimens from Patients with Rocky Mountain Spotted Fever.

Abundant spotted-fever–group rickettsiae (red area) appear in the endothelial cells of an arteriole in the dermis of Patient 4 (Panel A). Antigens and intact coccobacilli of *Rickettsia rickettsii* involve small vessels of the lung (Panel B), heart (Panel C), and kidney (Panel D) of Patient 7, who had a fatal case of Rocky Mountain spotted fever. (All panels were stained with hyperimmune rabbit anti–*R. rickettsii* antibody, alkaline phosphatase with naphthol fast-red substrate, and hematoxylin counterstain.)

Mountain spotted fever, and two reported a tick bite before the onset of illness. Disseminated intravascular coagulopathy developed in a two-year-old patient, who died, but serum and tissue specimens were not available for testing. A serum specimen obtained in 2003 from a 3-year-old patient showed titers of IgG antibody to *R. rickettsii* of 2048, and a specimen obtained in 2004 from a 23-year-old patient showed reciprocal titers of IgG and IgM to *R. rickettsii* of 32 and 1024, respectively, suggesting that the prior illnesses in these patients were probably Rocky Mountain spotted fever.

INVESTIGATION OF DOGS AND TICKS FROM PATIENTS' HOMESITES

The communities had large populations of dogs, many of which roamed freely among homesites. Serum specimens obtained from four dogs owned by Patients 3, 4, and 6 showed high titers of IgG antibodies reactive with *R. rickettsii* (≥16,384), indicating previous exposure to spotted-fever–group rickettsiae. Sixty-five partially or fully engorged *R. sanguineus* ticks were collected from dogs owned by some patients. *R. rickettsii* DNA was detected in one engorged adult *R. sanguineus* tick collected from a dog owned by Patient 3, and an isolate of *R. rickettsii* was cultured from this tick.

During the environmental assessment, nonengorged *R. sanguineus* ticks — 24 larvae, 753 nymphs, and 269 adults — were collected from the domestic environment of patients with confirmed Rocky Mountain spotted fever and from some neighboring community homesites. No *Dermacentor* species or ticks of other genera were found. Ticks were found in the immediate domestic environment, including in cracks in the stucco walls of homesites (Fig. 3A

Figure 3. The Domestic Environment of Patients' Homesites with Abundant *Rhipicephalus sanguineus* Populations.
Panels A and B show the stucco walls of the home of Patient 7, where numerous adult *R. sanguineus* ticks were found in crevices and cracks. Panel C shows the crawl space underneath the elevated house of Patient 6, where larval, nymphal, and adult *R. sanguineus* ticks were collected. Panel D shows the typical landscape of the communities involved in this investigation of Rocky Mountain spotted fever; the sparse, low vegetation and arid environment are common to eastern Arizona.

and 3B), in the crawl spaces under houses (Fig. 3C), and in discarded upholstered furniture that was placed outdoors and on which children and dogs were observed to rest. *R. rickettsii* DNA was detected with the use of PCR in 2 of 70 nonengorged adult *R. sanguineus* ticks (3 percent) collected from the domestic environment of Patient 7 and corroborated by culture isolation of *R. rickettsii* from these same ticks.

DISCUSSION

Our investigation of a focus of Rocky Mountain spotted fever in Arizona provides evidence that the common brown dog tick, *R. sanguineus*, may be a vector for Rocky Mountain spotted fever in some areas of the United States. Several lines of evidence strongly implicate *R. sanguineus* as the tick vector responsible for this hyperendemic focus of Rocky Mountain spotted fever. Ticks in all life stages were distributed abundantly in the environments in and around many of the patients' homes, and *R. rickettsii* was detected on PCR and cultured from engorged and nonengorged *R. sanguineus* adult ticks collected from patients' homesites. Neither *D. variabilis* nor *D. andersoni* ticks, the primary vectors for Rocky Mountain spotted fever in the United States, were found despite repeated entomologic evaluations at several times during the year. The hot, dry environmental conditions found in eastern Arizona (Fig. 3D) are not likely to support tick species other than *R. sanguineus*. The precise factors responsible for the magnitude of this outbreak remain to be determined, but they are probably related to locally high densities of *R. sanguineus* ticks and their close association with dogs and their proximity to humans in this area.

R. sanguineus is found worldwide and is widely distributed across North America, feeding primarily on dogs during each of its life stages.[13] *R. sanguineus* ticks bite humans infrequently, but immature *R. sanguineus* ticks are more likely than adults to feed on humans and have been shown to bite humans when their numbers are abundant.[14-17] Indeed, an *R. sanguineus* nymph was removed from a patient during this investigation, demonstrating that there is parasitism of humans by this tick species in this setting. Investigators in the 1930s determined in the laboratory that *R. sanguineus* was a vector of *R. rickettsii* and capable of efficient transstadial transmission (between developmental stages) and transovarial transmission of this agent.[18] Studies in Mexico during the 1940s identified *R. sanguineus* as a vector for pathogenic spotted-fever–group rickettsiae proven to be antigenically identical to *R. rickettsii*.[19,20] In addition, *R. sanguineus* is the principal vector of *R. conorii*, a pathogenic spotted-fever–group rickettsia species that causes disease in Europe, Africa, and Asia.[21] In these areas, a high prevalence of infestation by *R. sanguineus* ticks and close proximity of dogs and humans are risk factors for rickettsial infection.[21-25] Although previously suggested,[26,27] a role for this tick in the natural dynamics of transmission of *R. rickettsii* in the United States has not been demonstrated before this outbreak.

In this investigation, all patients reported contact with tick-infested dogs. Dogs serve as important transport hosts by carrying infected ticks close to their owners, as illustrated by numerous published reports of concurrent cases of Rocky Mountain spotted fever in dogs and their owners.[28-31] A possible role for dogs as natural reservoirs of *R. rickettsii* has not been thoroughly studied. Rickettsemia has been shown to be maintained in dogs for 6 to 10 days after experimental infection with *R. rickettsii*,[32-34] which could serve as a source of infection for feeding ticks. The factors contributing to the establishment of *R. rickettsii* in this new setting in Arizona may include dogs' functioning as reservoirs for the transmission of *R. rickettsii* among *R. sanguineus* ticks, the persistence of *R. rickettsii* within the tick population, or both. These possibilities should be explored more fully.

The incidence of Rocky Mountain spotted fever among children in this region (1800 cases per million persons 19 years of age or younger) is extremely high as compared with the average national annual incidence of only 5.6 cases per million persons for the same age group (National Electronic Telecommunication System for Surveillance, CDC, 1997–2002, unpublished data). There may be specific risk factors associated with the transmission of Rocky Mountain spotted fever that are unique to this age group; children were reported to associate closely with tick-infested dogs and to play frequently on discarded furniture that was found to harbor ticks. Young children may also have difficulty recognizing or reporting tick bites, which can result in prolonged attachment of the ticks and, possibly, increased rates of transmission of *R. rickettsii*.

It may not be possible to generalize the ecologic circumstances responsible for the infestation of *R. sanguineus* ticks in the Arizona communities to other regions of the United States where Rocky Mountain spotted fever is endemic; however, our investigation demonstrates that *R. sanguineus* can play a more important part in the natural history of *R. rickettsii* and the epidemiology of Rocky Mountain spotted fever than has been previously appreciated. The domestic habitat and broad distribution of *R. sanguineus* in the Western Hemisphere are a cause for concern about human exposure to this vector and the introduction of Rocky Mountain spotted fever into areas where it has not previously been recognized. Our findings suggest that other outbreaks and hyperendemic foci of Rocky Mountain spotted fever should be more closely investigated to determine whether *R. sanguineus* has a role in the transmission of the disease.

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CLINICAL PRACTICE

Postmenopausal Osteoporosis

Clifford J. Rosen, M.D.

This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

A 63-year-old woman presents with a history of acute low back pain. She had menopause at 44 years of age but never received postmenopausal hormone-replacement therapy. She reports a history of a Colles' fracture at the age of 60 years. Her mother sustained a hip fracture at 70 years of age. Lumbar-spine films reveal a new vertebral fracture. Dual-energy x-ray absorptiometry of the hip shows a bone mineral density T score of −1.3. How should her case be managed?

THE CLINICAL PROBLEM

Postmenopausal osteoporosis is a common disease with a spectrum ranging from asymptomatic bone loss to disabling hip fracture. The National Institutes of Health consensus conference defined osteoporosis as a disease of increased skeletal fragility accompanied by low bone mineral density (a T score for bone mineral density below −2.5) and microarchitectural deterioration.[1] In the United States, there are 1.5 million osteoporotic fractures per year, with an annual direct cost of nearly $18 billion.[2] It is predicted that the prevalence of fracture will increase by the year 2025, yet less than a quarter of all women who sustain an osteoporotic fracture currently receive appropriate treatment for osteoporosis.[3,4]

Fractures occur because of qualitative and quantitative deterioration in the trabecular and cortical skeleton. Bone quality cannot be measured clinically, but bone mineral density can be measured painlessly, quickly, safely, accurately, precisely, and relatively inexpensively; several methods are available, of which dual-energy x-ray absorptiometry is currently the most validated. Low bone mass at any skeletal site is associated with a substantially increased risk of fracture.[5,6] Other risk factors include advancing age, low body weight, maternal history of osteoporosis, the direction of a fall (a fall backward and to one side is most likely to result in a fracture), and most important, the presence of a previous fracture.[5-7] These and other risk factors for osteoporosis were reviewed in a recent Clinical Practice article in the *Journal*.[6]

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STRATEGIES AND EVIDENCE

OVERVIEW

A comprehensive management plan for osteoporosis includes evaluation of those at highest risk, exclusion of secondary causes of low bone mineral density, and selection of the appropriate treatment. A history of fragility fractures (unrelated to substantial trauma) in a postmenopausal woman strongly supports a diagnosis of osteoporosis, regardless of bone mineral density. Secondary causes such as primary hyperparathyroid-

ism, vitamin D deficiency due to low intake, lack of exposure to sunlight, or malabsorption, and multiple myeloma should be excluded, particularly if the z score (the number of standard deviations from the mean for an age- and sex-specific reference group) for bone mineral density is depressed (i.e., below −2.00). Biochemical markers of bone turnover such as N-telopeptide or osteocalcin rarely help in establishing a diagnosis or selecting treatment, although they may be useful in determining whether there is accelerated bone loss, particularly during the first few years of menopause.

Decision making should also take into account several caveats. Osteoporosis therapy can reduce the risk of fracture by as much as 50 percent, but some women have fractures despite treatment. Also, changes in lifestyle and the use of pharmacologic interventions are lifetime commitments, and therefore cost, compliance with a medication regimen, and safety must be considered in decisions on therapy.[8] Moreover, a substantial percentage of osteoporotic fractures occur in women who have T scores above −2.5. (A T score is the number of standard deviations the bone-mineral-density measurement is above or below the young-normal mean bone density.) In some cases, there is a substantial discrepancy between the spine and hip T scores. Thus, decisions with regard to treatment should not be based solely on bone mineral density.

PLANNING AN INTERVENTION STRATEGY

Therapy for postmenopausal osteoporosis is considered to be primary prevention when it is prescribed for those at risk without a T score below −2.5 or a history of fragility fracture and is considered to be treatment for those with established disease, including previous osteoporotic fracture, markedly reduced bone mineral density, or both.[9] The choice of an appropriate regimen will depend on whether the therapy is designed principally to prevent bone loss in patients with osteopenia (a T score between −1 and −2.5) or to reduce the likelihood of a first or subsequent fracture in patients with osteoporosis.

NONPHARMACOLOGIC OPTIONS

Calcium supplementation should be adjunctive treatment for all women with established osteoporosis and must be part of any preventive strategy to ameliorate bone loss. Increased calcium intake reduces the hyperparathyroidism associated with advancing age and can enhance mineralization of newly formed bone. A recent meta-analysis of 15 calcium intervention trials involving healthy women and postmenopausal women with osteoporosis demonstrated an increase of nearly 2 percent in spine bone mineral density after two years, although the risk of vertebral and nonvertebral fracture was not reduced to a statistically significant level.[10] A total calcium intake of 1200 to 1500 mg per day (through diet, supplements, or both) is recommended for all postmenopausal women.[9]

Vitamin D is essential for skeletal maintenance and enhancement of calcium absorption. Dietary insufficiency of this vitamin is a growing problem, with as many as two thirds of patients with hip fracture classified as having a deficiency of vitamin D (defined as a serum 25-hydroxyvitamin D [25(OH) vitamin D] level below 15 ng per milliliter [37.4 nmol per liter]).[11] Elderly persons with chronic conditions that require assisted-living situations are particularly vulnerable to vitamin D deficiency because of lack of adequate exposure to sunlight. One large trial showed a reduction of 33 percent in hip fracture among nursing home residents who were randomly assigned to receive calcium supplements and vitamin D, as compared with those given placebo.[12] In another trial, treatment with a single oral dose of 100,000 IU of vitamin D_3 every four months reduced nonvertebral fractures by nearly a third among elderly people who are able to walk.[13] Similarly, among older men and women in New England, calcium citrate (500 mg per day) and vitamin D_3 (700 IU per day) reduced the risk of nonvertebral fracture.[14] There is strong evidence that vitamin D supplementation enhances muscle strength and reduces the risk of falling.[15] Table 1 lists the various forms of calcium and vitamin D supplements.

Counseling with regard to avoidance of smoking and excessive alcohol intake is routinely warranted, particularly since smoking and alcohol intake have been linked in some studies to greater fracture risk.

Physical Activity

Bed rest or immobility due to other causes can result in rapid bone loss. Moreover, the number of falls and the percentage of falls that result in fracture increase with age.[16] A recent Cochrane meta-analysis found that muscle strengthening, balance training, assessment of the home for hazards, withdrawal of psychotropic medications, and the use of a multidisciplinary program to assess risk factors

Table 1. Calcium and Vitamin D Supplementation for Postmenopausal Women.*

Supplement	Preparation	Recommended Daily Total	Frequency of Doses	Comment
Calcium		1200–1500 mg	Two or three times daily	Side effects: nausea, constipation
Calcium carbonate		200–600 mg	Two or three times daily	Food enhances absorption
	Caltrate	600 mg	Twice daily	With or without vitamin D, at a dose of 200 IU; food enhances absorption†
	OsCal	250–600 mg	Two or four times daily	Fasting enhances absorption; with or without vitamin D
	Tums	200–500 mg	Two or three times daily	Available as chewable antacid tablets and pills
	Viactiv	500 mg	Twice daily	Available as flavored "chews"; with vitamin D†
Calcium lactate		42–84 mg	Five or six times daily	Requires taking many tablets very often
Calcium citrate				
	Citracal	200–500 mg	Two or four times daily	With or without vitamin D, at a dose of 200 IU; food enhances absorption†
Calcium phosphate	Posture	600 mg	Twice daily	Posture is the only calcium phosphate preparation available
Vitamin D	600–800 IU (15–20 μg) daily	Daily	Taken any time of the day	
	Multivitamin	400 IU per pill	Daily or twice daily	Good absorption; may contain vitamin D_2 or D_3
	Vitamin D	400 IU per pill	Daily or twice daily	Good absorption
	Calcium with vitamin D†	125–400 IU per pill	Daily or twice daily	The dose of vitamin D varies in different supplements
	Ergocalciferol (vitamin D_2)	50,000 IU per capsule	Once weekly	For vitamin D deficiency, vitamin D_3 is preferred
	Cholecalciferol (vitamin D_3)‡	50,000 IU per capsule	Once weekly	For vitamin D deficiency

* Adequate intake of vitamin D for older postmenopausal women, as established by the Institute of Medicine in 1997, is 600 IU daily; persons living in northern latitudes often have lower serum vitamin D levels and are thought to require 800 IU daily. The recommended daily totals are for elemental calcium and elemental vitamin D.

† Often calcium supplements contain vitamin D, but the dose and type of vitamin D vary (e.g., 125 IU to 400 IU per tablet). Similarly, vitamin D supplements often include calcium at various doses (e.g., 125 mg to 500 mg per tablet). Supplements need to be examined carefully by both the patient and the provider, so that proper doses are administered.

‡ Vitamin D_3 is preferred for replacement in persons with vitamin D deficiency, because it can be measured more accurately than D_2 and is absorbed better. However, high doses (e.g., 50,000 IU) can be difficult to obtain. Vitamin D_2 is derived from plant sources. It can be obtained from most formularies and pharmacies. Regardless of the type of vitamin D, treatment with high doses should not continue beyond three months and should be followed by a repeated measurement of the serum 25(OH)vitamin D level. If supplementation is successful in raising the serum level, a dose of 800 IU per day is used for maintenance. If supplementation is unsuccessful and the assay is valid, then consideration should be given to malabsorption, particularly gluten enteropathy.

all protect against falls.[17,18] Another approach is to pad the hip with a hip protector to reduce trauma during a fall; although patient compliance with this strategy is generally poor, when used properly, the strategy has been reported to reduce the risk of hip fracture.[19] Regular physical activity, including aerobic, weight-bearing, and resistance exercise, is effective in increasing bone mineral density of the spine and strengthening muscle mass in postmenopausal women, but there are no large trials establishing whether these interventions reduce the fracture risk.[20]

PHARMACOLOGIC OPTIONS

There is abundant evidence that an aggressive intervention program can reduce the risk of fracture and improve the quality of life among postmenopausal women with osteoporosis. Several pharmacologic options are available, and these can be classified according to their mechanism of action. The two main classes of drugs used to treat osteoporosis are antiresorptive agents (agents that block bone resorption by inhibiting the activity of osteoclasts) and anabolic agents (agents that stimulate bone formation by acting primarily on osteoblasts).

Table 2 is a review of agents for the treatment of osteoporosis that have been approved by the Food and Drug Administration.

Antiresorptive Agents

By suppressing osteoclast activity, antiresorptive agents slow the remodeling cycle, thereby enhancing mineralization of the bone matrix and potentially stabilizing the trabecular microarchitecture.[21] These agents increase bone mineral density in women with osteopenia or osteoporosis and reduce the risk of fracture in women with osteoporosis, although efficacy varies among the agents[22] (Table 2).

Postmenopausal Hormone-Replacement Therapy

Hormone-replacement therapy was once considered the primary therapy for postmenopausal women with osteoporosis. Estrogen slows bone resorption by blocking cytokine signaling to the osteoclast, increases bone mineral density, and reduces the incidence of new vertebral fractures by nearly 50 percent.[23] Treatment with low-dose conjugated estrogens (0.3 or 0.45 mg per day) or ultra-low-dose estradiol (0.014 mg per day) also increases bone mineral density, but the antifracture efficacy of these therapies has not been established.[24,25] Among women in the Women's Health Initiative trial, in

Table 2. Medications Approved by the Food and Drug Administration for the Treatment or Prevention of Postmenopausal Osteoporosis.*

Drug	Method of Administration and Dose	Reduction in Risk of Fracture	Side Effect	FDA Approval
Bisphosphonates	Oral		Esophagitis, myalgias	For treatment and prevention†
Alendronate	35–70 mg weekly, 5–10 mg daily	Vertebral, nonvertebral, and hip fracture		
Risedronate	30–35 mg weekly, 5 mg daily	Vertebral, nonvertebral, and hip fracture		
Ibandronate	150 mg monthly, 2.5 mg daily	Vertebral fracture	First dose‡	
SERM	Oral			For treatment and prevention
Raloxifene	60 mg daily	Vertebral fracture only	Hot flashes, nausea, DVT, leg cramps	
Anabolic agents	Subcutaneous, daily			
PTH (1–34) (teriparatide)	20 μg	Vertebral and nonvertebral fracture	Hypercalcemia, nausea, leg cramps	Approved for treatment only; generally used for severe osteoporosis
Calcitonin§	Subcutaneous or nasal, 100–200 IU	Vertebral fracture only	Nasal stuffiness, nausea	Approved for treatment only
Estrogens	Oral or transdermal		Risk of DVT, risk of cardiovascular disease, breast cancer	Approved for prevention only
Conjugated equine estrogens	Oral, 0.30–1.25 mg daily	Vertebral, nonvertebral, and hip fracture (at dose of 0.625 mg daily)		
17β-estradiol¶	Oral, 0.025–0.10 mg, or transdermal twice weekly	No data from randomized, controlled trials		For prevention only
	Ultra-low-dose (0.014 mg/day, given weekly)	No data available		

* All agents approved for treatment have demonstrated efficacy in reducing fractures, as determined in randomized, placebo-controlled trials with fracture as the primary end point. DVT denotes deep-vein thrombosis, SERM selective estrogen-receptor modulator, and PTH parathyroid hormone.
† There has been limited post-marketing experience with ibandronate for prevention.
‡ There may be a response to the first dose at 150 mg consisting of myalgias, joint aches, and low-grade fever, which is similar to a response to the first intravenous administration of bisphosphonates containing nitrogen.
§ The use of calcitonin is not generally recommended.
¶ A reduction in the risk of hip fracture has not been established for 17β-estradiol in a randomized, controlled trial.

those randomly assigned to receive conjugated estrogens, with or without a progestin, the reduction in hip fracture was 33 percent.[26] Discontinuation of estrogen results in measurable bone loss, although it is not certain whether discontinuation results in a greater fracture risk than continuation.[27] Recent concern about the nonskeletal risks associated with long-term use of estrogen (including the risk of breast cancer and the risk of cardiovascular disease), coupled with the availability of other drugs to treat osteoporosis has markedly lessened enthusiasm for hormone-replacement therapy in the treatment and prevention of osteoporosis.

Selective Estrogen-Receptor Modulators

A selective estrogen-receptor modulator such as raloxifene inhibits bone resorption through the same mechanism as do estrogens.[28] Raloxifene increases spine bone mineral density slightly and decreases the risk of vertebral fracture by 40 percent in women with osteoporosis, but it has no effect on the risk of nonvertebral fracture.[29] The risk of breast cancer is reduced with long-term use of raloxifene, although the drug is not approved for this indication.[30] New selective estrogen-receptor modulators are currently in phase 2 and 3 clinical trials.

Bisphosphonates

The bisphosphonates are the most widely prescribed antiresorptive agents and are often considered first-line therapy for the treatment of postmenopausal osteoporosis. These agents suppress resorption by inhibiting the attachment of osteoclasts to bone matrix and enhancing programmed cell death. First-generation bisphosphonates include etidronate and clodronate; neither drug is approved for the treatment of osteoporosis. Alendronate and risedronate, two second-generation nitrogen-containing bisphosphonates, have been shown in randomized trials to increase bone mineral density in postmenopausal women with osteopenia or osteoporosis; in women with osteoporosis, they have been shown to reduce the incidence of hip, vertebral, and nonvertebral fracture by nearly 50 percent, particularly during the first year of treatment.[22,31-34] As is the case with other antiresorptive drugs, increases in bone mineral density with alendronate or risedronate account for a small fraction of their antifracture efficacy.[8] Hence, follow-up measurements by dual-energy x-ray absorptiometry may substantially underestimate the reduction in fracture risk.

Recent data have shown that alendronate can be safely administered for at least seven years without adversely affecting bone strength.[35] Moreover, discontinuation of long-term (five years or more) alendronate therapy results in minimal bone loss over the ensuing three to five years.[27,35] Alendronate or risedronate once weekly has been shown to reduce the rate of drug-induced esophagitis, as compared with daily doses. In a recent one-year head-to-head study, alendronate increased spine and hip bone mineral density slightly more than risedronate, although the clinical significance of this finding is uncertain.[36]

Other bisphosphonates are available off-label or are being studied for the treatment of osteoporosis. Intravenous pamidronate has been used to treat women who cannot tolerate oral bisphosphonates; however, its efficacy in reducing fracture has not been established. Acute and delayed hypersensitivity reactions can occur with intravenous pamidronate, and its use is contraindicated in patients with vitamin D deficiency, since the drug can cause a precipitous drop in serum calcium levels.[37] In 2005, ibandronate, at a dose of 2.5 mg daily or 150 mg monthly, was approved by the Food and Drug Administration (FDA) for both the prevention and treatment of postmenopausal osteoporosis. Daily ibandronate has been shown to reduce significantly the incidence of vertebral fracture in women with osteoporosis and to reduce the incidence of nonvertebral fracture in women with severe osteoporosis (T score, below −3.0).[38] Intravenous zoledronate, which is approved for the treatment of malignant hypercalcemia, multiple myeloma, and skeletal metastases, can suppress bone resorption and increase bone mineral density in postmenopausal women for as long as one year after a single 4-mg dose.[39] Phase 3 trials are under way to evaluate the safety and efficacy of this drug in reducing osteoporotic fracture.

Calcitonin

Calcitonin is an endogenous peptide that partially inhibits osteoclast activity. Nasal calcitonin and subcutaneous calcitonin are approved for the treatment of postmenopausal osteoporosis. Although treatment of women with osteoporosis with nasal calcitonin at a dose of 200 IU per day has been shown to reduce the incidence of vertebral (but not nonvertebral) fracture in a single randomized trial, methodologic flaws in the study have limited enthusiasm for this agent.[40] In placebo-controlled studies, na-

sal calcitonin has reduced the pain associated with new spine fractures, although it is now considered preferable to treat osteoporosis with more potent agents and to manage pain separately.[41]

Strontium Ranelate

Strontium ranelate is orally administered and stimulates calcium uptake in bone while inhibiting bone resorption. In a randomized trial in postmenopausal women with osteoporosis, daily strontium ranelate reduced the risk of vertebral fracture by 40 percent.[42] However, a significant reduction in nonvertebral fracture was observed only in a post hoc analysis of a small subgroup of women.[42] This drug was recently approved by European regulatory agencies, but it is not currently approved by the FDA.

Anabolic Agents

The prototypical anabolic drug is sodium fluoride, which was widely used in the 1970s and 1980s because of its ability to stimulate the formation of new bone. However, a randomized trial in 1990 established that despite dramatic increases in bone mineral density, the risk of nonvertebral fracture actually increased with the use of fluoride.[43] In 2002, synthetic parathyroid hormone (1–34) (teriparatide) was the first anabolic agent approved by the FDA for the treatment of postmenopausal osteoporosis. Unlike antiresorptive agents, parathyroid hormone stimulates bone remodeling by increasing bone formation. In a large randomized trial involving postmenopausal women with severe osteoporosis, 20 μg of parathyroid hormone per day administered subcutaneously markedly increased bone mineral density and reduced vertebral and nonvertebral fractures by more than 50 percent.[44] However, the trial was stopped after 20 months because of concern about the development of osteosarcoma in rats treated with high doses of parathyroid hormone (1–34). As a result, a "black-box" warning was added to the teriparatide label. However, retrospective studies have found no association between osteosarcoma and primary or secondary hyperparathyroidism in humans, and no cases of osteosarcoma have been reported in the more than 200,000 patients treated with parathyroid hormone. The current recommendation is that parathyroid hormone therapy should be limited to persons with moderate-to-severe osteoporosis and that the duration of therapy should not exceed two years. Parathyroid hormone (1–34) is well tolerated, although mild but asymptomatic hypercalcemia (i.e., a serum calcium level between 10.5 and 11.0 mg per deciliter [2.6 and 2.8 mmol per liter]) can occur rarely. Cost and the requirement of subcutaneous administration are major limiting factors.

Combination Therapy

Although studies have suggested that combining antiresorptive agents may slightly increase bone mineral density as compared with monotherapy, there are no data to indicate that combination therapies are superior for reducing the risk of fracture.[27,45] There is also no evidence that combining parathyroid hormone with an antiresorptive drug results in additive or synergistic effects,[46,47] but concurrent use of cyclic parathyroid hormone (i.e., daily parathyroid for 3 months followed by no treatment for 3 months for a period of 15 months) with alendronate may be just as effective as daily parathyroid hormone with alendronate.[48] Nevertheless, bone loss will occur after the discontinuation of parathyroid hormone, but it can be prevented if this therapy is followed by treatment with an antiresorptive drug such as alendronate.[49,50]

AREAS OF UNCERTAINTY

The optimal timing and type of preventive therapy are still not clearly defined. Many postmenopausal women have T scores between −1.0 and −2.5 but no other risk factors. Postmenopausal hormone-replacement therapy, once considered the best preventive approach for these women, is no longer recommended in light of the associated risks reported in the Women's Health Initiative trial.[26] Bisphosphonates prevent bone loss in women with osteopenia and can be used as prophylaxis, but cost-effectiveness and concerns about the effects on skeletal mineralization over decades may be limiting factors.[22] Studies such as the extension of the Fracture Intervention Trial (evaluating alendronate) have provided some reassurance with regard to long-term use.[35]

Also uncertain is the appropriate care for patients who continue to have fractures despite aggressive pharmacologic intervention. Whether new agents such as the synthetic antibody to the receptor activator of nuclear factor-κB ligand (AMG 162) or strontium ranelate will be effective in preventing new fractures in such patients needs to be tested.[42,51] Finally, controversy persists about the use of vertebroplasty or kyphoplasty, procedures that introduce material to expand compressed vertebrae

Table 3. Recommended Regimens for the Prevention and Treatment of Postmenopausal Osteoporosis.*

Organization	Whom to Treat	Nonpharmacologic Intervention	Pharmacologic Intervention
National Osteoporosis Foundation	T score below –2.0 with no risk factors T score below –1.5 with one or more risk factors Any spine or hip fracture	1200 mg calcium daily 400–800 IU vitamin D daily Regular weight-bearing exercise	Antiresorptive agents or anabolic agents
American Association of Clinical Endocrinology	T score below –2.5 T score below –1.5 with fractures	1200 mg calcium daily 400–800 IU vitamin D daily Weight-bearing physical activity	Antiresorptive or anabolic agents
U.S. Surgeon General's Pyramid Approach†	No recommendations	1200 mg calcium daily 600–800 IU vitamin D daily Regular weight-bearing activity (30 minutes daily) Strength and balance training	Antiresorptive agents or anabolic agents

* Data in this table are from the National Osteoporosis Foundation (2003),[54] Hodgson et al. (2001),[55] and the Office of the Surgeon General (2004).[9] T scores are the number of standard deviations the bone-mineral-density measurement is above or below the young-normal mean bone mineral density.

† The pyramid approach consists, in ascending order, of lifestyle changes, the identification of a secondary cause of osteoporosis, and pharmacotherapy.

and reduce the pain associated with new fractures. Both the absence of randomized, placebo-controlled trials and concerns about the mechanical strength of adjacent vertebrae after these procedures preclude making recommendations for their use.[52,53]

GUIDELINES

Several professional societies and government agencies have provided guidelines for treatment options (Table 3).

SUMMARY AND RECOMMENDATIONS

A careful history taking and physical examination that address risk factors for or signs of osteoporosis (particularly previous fragility fractures, height loss, or both, as well as possible secondary causes of bone loss) combined with measurement of bone mineral density should guide therapeutic decisions. Given the high prevalence of low levels of 25(OH) vitamin D in women with osteoporosis, measurement of a serum 25(OH) vitamin D level by a reliable laboratory is reasonable. Treatment plans for a patient such as the woman in the vignette should include calcium supplementation to a level of at least 1200 mg per day and 800 IU of vitamin D, as well as pharmacologic therapy. I would start with an oral bisphosphonate (alendronate or risedronate) once weekly or ibandronate once monthly, given the documented reductions in the incidence of hip and vertebral fracture with these agents. Alternatively, one could consider parathyroid hormone (1–34) for two years if a patient cannot tolerate a bisphosphonate or has had multiple fractures, although with this regimen, cost and compliance need to be taken into consideration. Irrespective of the choice of therapy, careful follow-up, with attention to pain, lifestyle, and risk factors for future fracture, is necessary.

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REVIEW ARTICLE

MECHANISMS OF DISEASE

Retinoid X Receptor Heterodimers in the Metabolic Syndrome

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The metabolic syndrome, also known as syndrome X, is characterized by abdominal obesity, atherogenic dyslipidemia, hypertension, insulin resistance, inflammation, and prothrombotic states.[1] Diagnostic of the metabolic syndrome are abnormalities in three or more of the clinical criteria of the Adult Treatment Panel III of the National Cholesterol Education Program, which include the following: a waist circumference of more than 102 cm in men and more than 88 cm in women; a triglyceride level of 150 mg per deciliter or more; a level of high-density lipoprotein (HDL) cholesterol of less than 40 mg per deciliter in men and less than 50 mg per deciliter in women; a blood pressure of 130/85 mm Hg or more; and a fasting glucose level of 110 mg per deciliter or more.[2] The age-adjusted prevalence of this syndrome in the United States from 1988 to 1994 was estimated to be 23.7 percent, and the scope of the public health challenge it poses is likely to increase.[3] The major sequelae are cardiovascular disease and type 2 diabetes mellitus, but the syndrome also increases the risk of polycystic ovary syndrome, fatty liver, cholesterol gallstones, asthma, sleep disturbances, and some forms of cancer. A prospective study of Finnish men reported a connection between the metabolic syndrome and an increased risk of death associated with cardiovascular disease and all-cause mortality[4] — a finding that underscores the severity of this disease.

The pathogenesis of the metabolic syndrome is thought to involve a complex interaction of multiple factors, which include obesity and abnormal fat distribution; insulin resistance; hepatic, vascular, and immunologic factors; and lifestyle and genetic contributions.[1] In addition to behavioral therapies that promote weight reduction through exercise and dietary modification, management of the metabolic syndrome includes a combination of medical therapies targeted to reduce specific metabolic risk factors.[5] Statins and fibric acid derivatives (fibrates) are effective first-line treatments for atherogenic dyslipidemia and have been shown to reduce the risk of cardiovascular disease.[2] Combination therapy with a statin and a fibrate prevents the lowering of HDL cholesterol that is observed with the use of a statin alone and can improve abnormal serum lipoprotein profiles. The ability of statins and fibrates to induce severe myopathy, a toxic effect that is more frequent in combination treatment, limits their use in some patients.[6] Metformin and thiazolidinediones improve insulin sensitivity, but it is unknown if they reduce the risk of cardiovascular disease, and there are dose-limiting toxic effects. Experience with medical therapies highlights the potential of restoration of individual metabolic abnormalities in the treatment of the metabolic syndrome. Although numerous treatment options are available, the syndrome and its long-term sequelae often prove refractory to these interventions.

Intense interest in the development of drugs with new mechanisms of action for the metabolic syndrome has focused attention on nuclear receptors. Nuclear receptors are transcription factors that serve as intracellular receptors for endocrine hormones and

dietary lipids. In contrast to extracellular receptors, which bind to peptide ligands (e.g., growth factors and insulin) and activate cytoplasmic kinase cascades, nuclear receptors interact directly with lipophilic ligands and regulate expression of target genes. The retinoid X receptor (RXR), a member of the nuclear-receptor superfamily, is a common binding partner for a subgroup of other nuclear receptors. The resulting functional complex of one RXR molecule with one distinct nuclear-receptor molecule is known as a heterodimer. Drugs that target RXR and its heterodimerization partners are already in clinical use for the treatment of cancer, dermatologic diseases, endocrine disorders, and the metabolic syndrome (Table 1).

Like the lipid abnormalities in familial combined hyperlipidemia, moderately elevated levels of plasma triglycerides and cholesterol occur in the metabolic syndrome. Homeostatic regulation of lipid metabolism requires cellular sensors that can monitor the concentration of bioactive lipids and coordinate the enzymatic cascades that regulate lipid synthesis and catalysis. Abnormal function of the lipid-sensing system not only underlies dyslipidemia but also contributes to deficiencies in carbohydrate metabolism and other integrated physiologic processes. Recent work has shown that RXR and its heterodimerization partners bind to a variety of ligands derived from cholesterol, fatty acids, and fat-soluble vitamins and regulate target genes that mediate transport and catalysis of dietary lipids. The focus of this review is on new advances in understanding the function of RXR heterodimers in normal intermediary metabolism and in the pathophysiology of the metabolic syndrome. We also consider the promising findings about how drugs that target RXR heterodimers may be used in the management of the metabolic syndrome.

REVERSE ENDOCRINOLOGY OF RXR HETERODIMERS

Nuclear receptors that function as RXR heterodimers were cloned on the basis of their homology to the steroid hormone receptors and were characterized before their ligands were known. All members of the nuclear-receptor superfamily share a canonical domain structure (a structure shared by several proteins) that includes an N-terminal activation domain and conserved DNA and ligand-

Table 1. Approved Drugs Targeting RXR Heterodimers.*

Target Receptor	Drug	Compound Class	Brand Name	Indication
RXRα, RXRβ, and RXRγ	Bexarotene	Rexinoid (e.g., LG1069)	Targretin	Refractory cutaneous T-cell lymphoma
RARα, RARβ, and RARγ; RXRα, RXRβ, and RXRγ	Alitretinoin	Retinoid (e.g., 9-*cis*-retinoic acid)	Panretin	Kaposi's sarcoma (topical only)
RARα, RARβ, and RARγ	Tretinoin	Retinoid (e.g., all-*trans*-retinoic acid)	Retin-A, Renova, Vesanoid	Acute promyelocytic leukemia, acne
RARα, RARβ, and RARγ	Isotretinoin	Retinoid (e.g., 13-*cis*-retinoic acid)	Accutane	Severe nodular acne
Vitamin D receptor	Calcitriol	1,25-dihydroxyvitamin D_3	Rocaltrol, Calcijex	Hypocalcemia due to chronic renal failure and hypoparathyroidism
Vitamin D receptor	Ergocalciferol	Vitamin D_2	Calciferol	Vitamin D–resistant rickets, hypoparathyroidism, familial hypophosphatemia
TRα and TRβ	Levothyroxine	Thyroid hormone (e.g., L-thyroxine or T_4)	Levo-T, Unithroid, Levothyroid, Levoxyl, Synthroid	Hypothyroidism, euthyroid goiters, Hashimoto's thyroiditis
PPARγ	Pioglitazone	Thiazolidinedione	Actos	Type 2 diabetes mellitus (monotherapy or combination therapy)
PPARγ	Rosiglitazone	Thiazolidinedione	Avandia	Type 2 diabetes mellitus (monotherapy or combination therapy)
PPARα	Fenofibrate	Fibrate	Tricor	Types IIa, IIb, IV, and V hyperlipidemia
PPARα	Gemfibrozil	Fibrate	Gemfibrozil, Gemcor, Lopid	Types IIb, IV, and V hyperlipidemia

* Drugs approved by the Food and Drug Administration that target RXR or its heterodimeric partners, and their clinical indications, are listed.

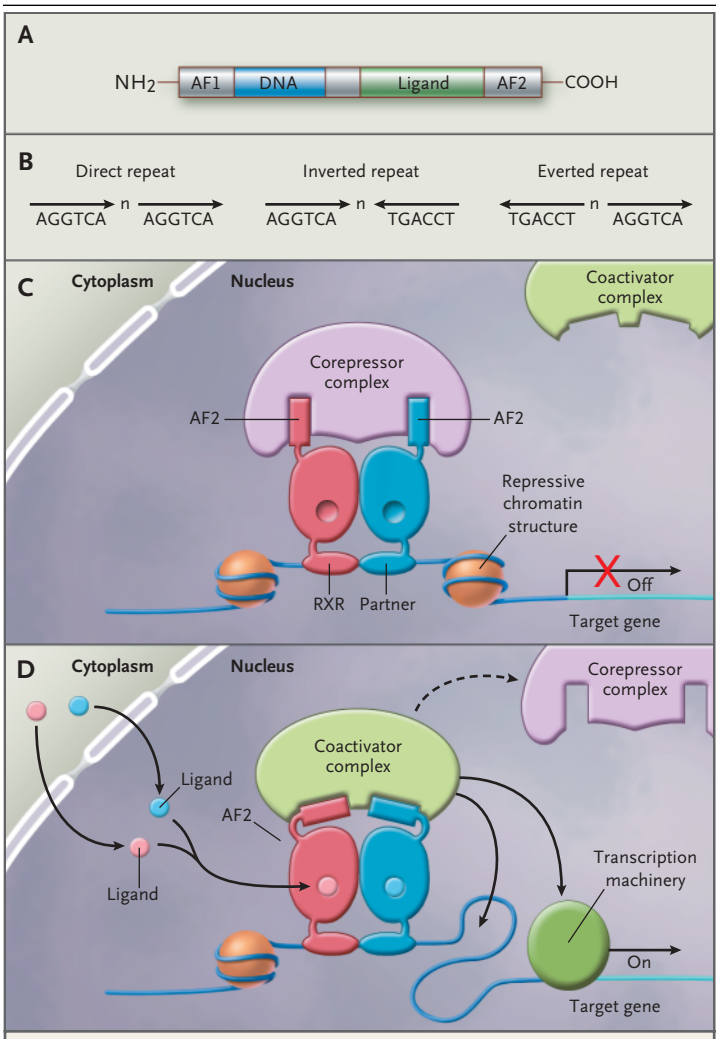

Figure 1. Nuclear Receptors as Ligand-Dependent Transcription Factors.

Panel A shows the canonical structure of the nuclear receptor, which includes N-terminal activation function 1 (AF1), DNA binding, ligand binding, and C-terminal AF2 domains. Response elements in the nuclear receptor can be configured as either direct, inverted, or everted repeats of the hexad core sequence AGGTCA (Panel B). The number of nucleotides between the two core elements (n) confers additional specificity. As shown in Panels C and D, RXR heterodimers constitutively bind to response elements in the promoter regions of target genes. In Panel C, in the absence of agonist ligand, the AF2-domain conformation promotes receptor interaction with corepressors. The multiple-subunit corepressor complex stabilizes repressive local chromatin structure and blocks access of the transcription machinery (red X) to the promoter. As shown in Panel D, ligands diffuse across the nuclear membrane and bind to receptor ligand-binding domains. Ligand binding triggers a conformational change in the AF2 domain, which destabilizes corepressor interaction and promotes coactivator binding. Multiple-subunit coactivator complexes activate local chromatin structure and recruit the transcription machinery to the promoter, where target-gene transcription commences.

binding domains (Fig. 1A). Nuclear receptors function as ligand-dependent transcription factors by binding to specific DNA sequences called response elements within the regulatory regions of target gene promoters. Each response element consists of a consensus sequence (AGGTCA) that is configured as a single element or as two tandem elements in a direct, everted, or inverted repeat, which permits binding of nuclear receptors as monomers, homodimers, or heterodimers (Fig. 1B).[7] A number of nuclear receptors must interact with RXR to form heterodimers that can bind to DNA response elements and activate target gene expression.[8,9] Structural studies of various nuclear-receptor ligand-binding domains have revealed a scaffold composed of 12 alpha helixes with a central hydrophobic pocket that directly binds a number of hormonal, lipid, and synthetic ligands. Analysis of structure–activity relationships for many agonist-bound nuclear receptors shows that helix 12, the AF2 helix, adopts a strikingly similar active conformation in all nuclear receptors.[10] Nuclear receptors activate or repress target gene expression through ligand-dependent interactions with accessory proteins, known as coactivators and corepressors. These cofactors form multiple-subunit complexes that modify local chromatin structure and recruit the transcription machinery to target gene promoters.[11] The coactivators and corepressors sense the ligand-binding status of nuclear receptors by recognizing alternative AF2 conformations (Fig. 1C and 1D). In addition to providing a mechanism for ligand-dependent transcriptional regulation, cofactors allow coordinated regulation of nuclear-receptor signaling. For example, specific cofactors, such as the peroxisome-proliferator–activated receptor (PPAR) γ coactivator 1, appear to have important roles in metabolic control by nuclear receptors.[12]

A 15-year effort to identify the ligands and physiologic roles of the RXR heterodimers has revealed a central role for these receptors as the body's lipid sensors. This ongoing research effort is known as "reverse endocrinology" because it originated with the characterization of cloned-receptor sequences as opposed to classic endocrine bioassays.[13] Together, the concerted application of the numerous methods can be described as a nuclear-receptor "discovery cycle," in which each step of the cycle may be used autonomously to lead to important discoveries (Fig. 2).

Initially, RXR heterodimer receptors are fed into the cycle by identifying their lipophilic, small-molecule agonists (i.e., ligands). Agonists resulting from such screens can then be used to identify target genes whose expression is regulated by the receptor. Once the physiologic role of a receptor has been implicated by its tissue distribution, ligand identity, and target genes, the receptor can be further tested with the use of genetic studies of loss and gain of function in animal models. Such experiments provide the rationale for translational research in human disease and, ultimately, for the development of nuclear-receptor ligands as therapeutic drugs. Efforts to create RXR heterodimer agonists with reduced adverse effects are analogous to the successful development of tissue-selective estrogen-receptor modulators (e.g., tamoxifen and raloxifene).[14] Continued refinement of lead pharmacologic compounds through the discovery cycle can provide new biologic insights and candidate drugs.

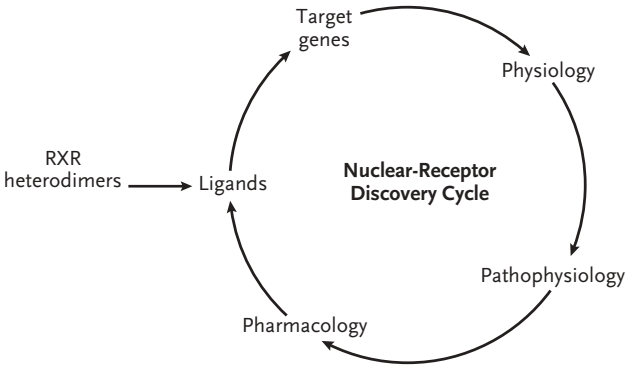

Figure 2. Nuclear-Receptor Discovery Cycle.
Concerted application of numerous approaches has clarified the physiologic and pathologic roles of nuclear receptors and has created new pharmacologic opportunities.

This discovery cycle has already revealed a central role for RXR heterodimers as cellular lipid sensors that might participate in the pathogenesis of metabolic disease (Table 2 and Fig. 3).[15] It is important to note that although nuclear receptors link lipid binding to the regulation of genes involved in the maintenance of metabolic homeostasis, the potentially protective roles of these receptors in disease are a consequence of pathologic conditions (e.g., a lipid-rich diet). As a result, pharmacologic manipulation of receptor activity can be expected to be associated with both beneficial and adverse metabolic effects in various contexts. We will use the discovery cycle as a framework to discuss the potential role of selected, individual RXR heterodimers in the metabolic syndrome. Although other RXR heterodimers (e.g., retinoic acid receptors and vitamin D receptor) are therapeutically important (Table 1), their involvement in the metabolic syndrome has not been shown, and they will not be discussed further.

RXRs: PARTNERS IN SIGNALING

The discovery that RXRs can be activated by 9-*cis* retinoic acid, an endogenous vitamin A derivative that is now in clinical use (Table 1), represents the first successful implementation of the discovery cycle and validates the reverse endocrinology concept.[8] Nuclear receptors that partner with RXR to form a heterodimer can be divided into functionally distinct permissive and nonpermissive groups (Table 3). RXR heterodimers that are formed by RXR and a permissive binding partner (e.g., PPARs, liver X receptors, and farnesoid X receptor [FXR]) can be activated by agonists for both RXR and the partner receptor.[16] For example, an RXR–PPAR heterodimer can be activated by both RXR and PPAR agonists independently or together to cause a synergistic activation. In contrast, RXR heterodimers that contain nonpermissive partners (e.g., vitamin D receptor and thyroid hormone receptor) can be activated only by the partner receptor's agonist but not by an RXR agonist. Permissive partners serve as receptors for dietary lipids and may allow RXR activation in order to establish steady-state expression levels for metabolic enzymes and transporters. In contrast, nonpermissive partners function primarily as hormone receptors and may inhibit RXR activation in order to place target genes under tight hormonal control. In this way, a small change in hormone concentration substantially alters the level of target gene expression, a property that meets the requirements of endocrine physiology.

The ability of RXR agonists to regulate target genes of multiple permissive partners implies that in vivo such compounds may have pharmacologic use as panagonists of several metabolically important pathways.[17] The observation that liver-specific deletion of RXR in mice results in abnormalities in all metabolic pathways regulated by RXR hetero-

Table 2. Nuclear Receptor Regulation of Lipid, Cholesterol, and Bile-Acid Metabolism.*

Nuclear Receptor	Tissue Distribution	Ligand	Physiologic Function	Associated Disease Process†
Retinoid X receptors				
RXRα, RXRβ, and RXRγ	Ubiquitous	9-*cis*-retinoic acid, DHA, rexinoids‡	Common heterodimer partner	Same as for heterodimeric partners
Peroxisome-proliferator–activated receptors				
PPARα	Liver, heart, muscle, kidney	Fatty acids, fibrates‡	Fatty-acid oxidation	Dyslipidemia, diabetic cardiomyopathy
PPARγ	Adipose, macrophage, muscle	Fatty acids, eicosanoids, thiazolidinediones‡	Adipogenesis, lipid storage	Insulin resistance, obesity, metabolic syndrome
PPARδ	Ubiquitous	Fatty acids	Fatty-acid oxidation, energy expenditure	Dyslipidemia, obesity
Liver X receptors				
LXRα and LXRβ	LXRα: liver, adipose tissue, kidney, intestine; LXRβ: ubiquitous	Oxysterols	Cholesterol homeostasis, fatty-acid synthesis	Atherosclerosis, dyslipidemia
Farnesoid X receptor				
FXR	Liver, intestine, kidney	Bile acids	Bile-acid homeostasis	Cholestasis, gallstone disease, dyslipidemia
Thyroid hormone receptors				
TRα and TRβ	Ubiquitous	Thyroid hormone‡	Metabolic rate, neural development, cholesterol metabolism	Cardiac dysfunction, dyslipidemia, obesity

* Tissue distribution, ligands, physiologic functions, and pathologic roles of RXRs and their heterodimeric partners involved in metabolic regulation are shown. DHA denotes docosahexaenoic acid.
† Increased or decreased activity of the indicated receptor contributes to the pathophysiology of the disease listed. In some cases, a receptor agonist or antagonist might be an effective therapy for the disease process.
‡ Indicated are ligands currently used in the clinic — rexinoids for cancer, fibrates for dyslipidemia, thiazolidinediones for type 2 diabetes mellitus and the metabolic syndrome, and thyroid hormone for deficiency states.

dimers underscores the central, pleiotropic role of RXR.[18] Although RXR agonists have therapeutic value (Table 1) and might offer enhanced potency through panactivation of permissive heterodimers, this advantage is likely to be offset by poor selectivity. In addition, the propensity of RXR agonists to induce hypertriglyceridemia in animals and humans[19] indicates that targeting the heterodimeric partners of RXRs is likely to result in more suitable candidates for drug therapy.

PPARs: FATTY-ACID SENSORS

PPARα

The PPARs are nuclear receptors that bind to fatty-acid–derived ligands and activate the transcription of genes that govern lipid metabolism. The primary sites of action of PPARα, which recognizes monounsaturated and polyunsaturated fatty acids and eicosanoids, are liver, heart, muscle, and kidney.[20,21] Consistent with its role in regulating fatty-acid metabolism, PPARα activates a program of target gene expression involved in fatty-acid uptake (fatty-acid–binding protein), beta oxidation (medium-chain acyl-CoA dehydrogenase, carnitine palmitoyltransferase I, and acyl-CoA oxidase), transport into peroxisomes (ATP-binding cassette transporters D2 and D3), and omega oxidation of unsaturated fatty acids (cytochrome P-450 4A1 and 4A3).[22-25]

In the fasting state, PPARα is activated by adipose-derived fatty acids, thereby enhancing the generation of ketone bodies through hepatic fatty-acid oxidation. Fasting PPARα-deficient mice have severe hypoglycemia and hypoketonemia, fatty liver, and elevated plasma nonesterified fatty acids, revealing the important role of this receptor in the hypoglycemic response.[24,26] PPARα-deficient mice that are fed a high-fat diet are unable to up-regulate fatty-acid catalysis and develop hepatic steatosis in the absence of obesity.[27] In cardiac muscle, PPARα activation decreases glucose uptake and causes a shift from glucose use to fatty-acid oxidation.[28] For

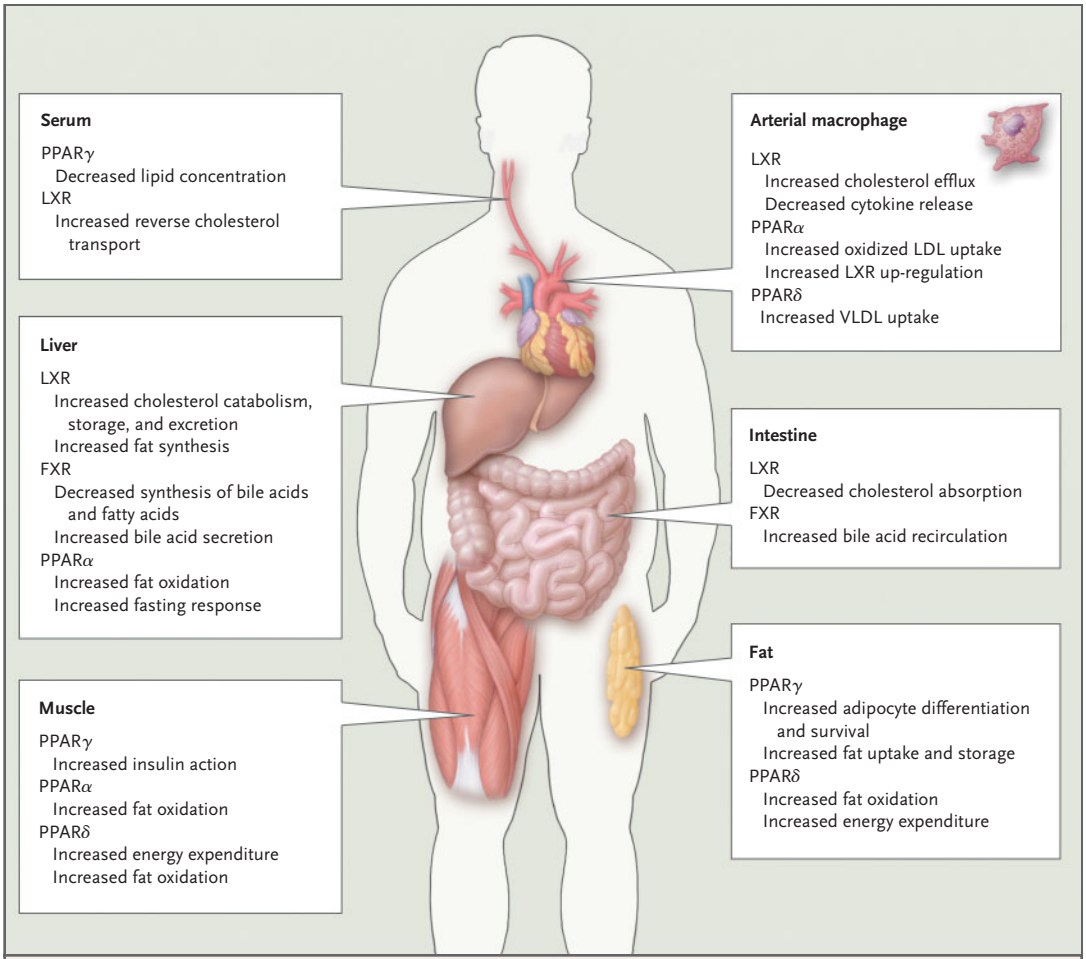

Figure 3. Regulation of Cholesterol and Lipid Handling in Metabolic Organ Systems by Nuclear Receptors.

The major actions of RXR heterodimer partners at sites that participate in intermediary metabolism, absorption, energy storage, energy expenditure, and lipid transport are indicated. Dysfunction in these organ systems contributes to the pathogenesis of the metabolic syndrome. LDL denotes low-density lipoprotein cholesterol, and VLDL very-low-density lipoprotein cholesterol.

this reason, supraphysiologic activation of PPARα in the heart brings about lipid accumulation, ventricular hypertrophy, and systolic dysfunction — a phenotype that resembles diabetic cardiomyopathy. Taken together, mouse models suggest that PPARα functions to increase fatty-acid use in the fasting state and that in the pathophysiologic context of a high-fat diet, PPARα-induced fatty-acid catabolism might prevent hypertriglyceridemia. Consistent with this prediction, an activated variant of PPARα (Leu162Val) is associated with low serum triglyceride levels and reduced adiposity.[29]

The finding that fibrate drugs, such as fenofibrate and gemfibrozil, act as PPARα agonists makes this receptor an attractive target in the treatment of atherogenic dyslipidemia.[30,31] Fibrates, which reduce the risk of cardiovascular disease in patients with hypertriglyceridemia and a low-to-normal level of serum HDL cholesterol, most likely decrease serum triglyceride levels and cause slight increases in levels of serum HDL cholesterol by PPARα-mediated activation of fatty-acid beta oxidation.[32] A well-known side effect of synthetic PPARα agonists in rodents is hepatomegaly due to proliferation of peroxisomes, specialized organelles for fatty-acid beta oxidation.[27,33] Fortunately, these effects are rodent-specific and are not observed in humans. Selective PPARα agonists that increase fatty-acid catabolism without causing lipid accumulation in the heart might be effective treatments for dyslipidemia.

Table 3. Ligand Permissivity Associated with Function of RXR Heterodimer.*

Variable	Permissive	Nonpermissive
Receptors	PPARs, LXRs, FXR	VDR, TRs
Ligand	Dietary lipids	Endocrine hormones
Ligand affinity	Micromolar to nanomolar	Nanomolar to picomolar
Physiologic range of ligand	Broad	Narrow
Ligand regulation	Feed-forward	Feedback

* Permissive RXR heterodimer partners bind to dietary lipids with low affinity and activate feed-forward enzymatic cascades that regulate ligand catabolism. Nonpermissive RXR partners are high-affinity endocrine receptors that regulate ligand concentration by negative feedback of hormone synthesis. Although pathologic states result when the concentration of hormonal ligands occurs outside of narrow limits, the physiologic range of dietary lipid concentration is broader. VDR denotes vitamin D receptor and TR thyroid hormone receptor.

PPARγ

PPARγ is expressed in adipocytes, macrophages, and muscle, where it regulates development, lipid homeostasis, and glucose metabolism. Endogenous PPARγ agonists include fatty acids and eicosanoids.[20,34,35] The PPARγ genetic program includes target genes involved in the uptake of glucose in muscle (c-Cbl associated protein and glucose transporter 4), lipid metabolism (scavenger receptor, adipocyte-fatty-acid–binding protein, lipoprotein lipase, fatty-acid–binding protein, acyl-CoA synthetase, and CYP4B1), and energy expenditure (glycerol kinase and uncoupling proteins 2 and 3).[36-44] Mice lacking PPARγ in the germ line are embryonic lethal because of a placental defect,[45-47] but creation of conditional PPARγ knockouts and the use of in vitro fibroblast-differentiation assays have confirmed the essential role of PPARγ in adipocyte differentiation and survival.[45,47,48] In addition, specific deletion of the *PPARγ* gene in fat and muscle causes insulin resistance, demonstrating the importance of this receptor in peripheral insulin sensitivity.[48,49]

It is interesting to note that heterozygous PPARγ knockout mice have improved insulin sensitivity and are not susceptible to the insulin resistance and obesity associated with a high-fat diet.[46] This finding is consistent with the therapeutic action of PPARγ partial agonists, such as the thiazolidinediones, and confirms the notion that partial activation of PPARγ is required to promote nominal, but not excessive, adipose storage depots and thereby maintain a proper insulin response. Possible mechanisms of PPARγ-induced insulin sensitivity include increased lipid uptake and storage, leading to decreased free fatty acids and serum triglycerides, suppression of hepatic gluconeogenesis, and a small contribution toward increased uptake of glucose by adipose tissues. PPARγ activation also increases energy expenditure by inducing a futile cycle of triglyceride synthesis from free fatty acids and increasing uncoupled respiration through uncoupling proteins.[44]

In addition to regulating glucose and lipid metabolism, PPARγ is a potential modifier of atherogenesis. Signaling through PPARγ, components of oxidized low-density lipoprotein (LDL) increase expression of the scavenger receptor CD36, resulting in lipid accumulation in macrophages.[50,51] PPARγ also activates the macrophage LXR-ABCA1 cholesterol efflux pathway,[52] which may explain the finding that PPARγ ligands inhibit the formation of atherosclerotic lesions in LDL-receptor–deficient mice.[53]

Human genetics has provided independent corroboration of the central role of PPARγ in the metabolic syndrome.[54] Dominant negative mutations in PPARγ are the cause of monogenic disease with features of the metabolic syndrome, including severe insulin resistance, type 2 diabetes mellitus, and hypertension.[55] The PPARγ Pro12Ala variant is associated with a low body-mass index and insulin sensitivity, and it appears to protect against the metabolic syndrome.[56]

The landmark finding that the thiazolidinedione class of insulin sensitizers, including rosiglitazone and pioglitazone (Table 1), function as high-affinity PPARγ agonists has validated the efficacy of PPARγ modulation in treating the metabolic syndrome.[57] Although thiazolidinediones have become important first-line agents for increasing insulin sensitivity, adverse effects including weight gain, adipogenesis, and toxic effects in the liver have limited their use. In addition, recent data indicating that PPARγ agonists have carcinogenic potential in rodents have prompted the Food and Drug Administration to require two-year carcinogenicity studies in rodents in its consideration of new drugs in this class. The effort to design safe and selective PPARγ modulators that retain an insulin-sensitizing function without activating adipocyte differentiation and lipid accumulation is ongoing.[58] Second-generation PPARγ agonists have the promise to improve multiple metabolic measures and reduce the risk of cardiovascular disease in patients with the metabolic syndrome.

PPARδ

PPARδ is expressed ubiquitously and is activated by fatty acids and components of very-low-density lipoprotein (VLDL).[59,60] PPARδ target genes control beta oxidation in murine brown fat (long-chain and very-long-chain acyl-CoA synthetase, long-chain and very-long-chain acyl-CoA dehydrogenase, and acyl-CoA oxidase), energy expenditure (uncoupling proteins 1 and 3), and lipid storage (macrophage adipose differentiation–related protein).[61,62] Similar to conventional targeting of PPARγ, most PPARδ knockout mice die in midgestation as a result of defects related to the placenta. Surviving mice show markedly decreased adipose tissue, a finding that is not recapitulated in adipose-specific knockout mice and suggests a requirement for PPARδ in peripheral tissues.[63] Genetic activation of PPARδ in adipocytes and treatment with a synthetic PPARδ agonist result in increased beta oxidation of fatty acids, energy expenditure, and resistance to diet-induced obesity.[61] PPARδ also mediates transcriptional responses to VLDL-derived triglycerides in macrophages.[60]

In the pathophysiological context of a high-fat diet, PPARδ could function to increase adipose fatty-acid catabolism and may play a role in VLDL-induced lipid accumulation in atherosclerotic foam cells. A high-affinity synthetic PPARδ agonist has been shown to increase HDL and decrease LDL, triglycerides, and fasting insulin in obese rhesus monkeys.[64] These studies suggest that therapeutic activation of PPARδ has the potential to decrease diet-induced obesity without activating the PPARγ-dependent adipogenic program.

LXRs: STEROL SENSORS

The LXRs are nuclear receptors that bind oxidized cholesterol derivatives (oxysterols) such as 24(S),25-epoxycholesterol.[65] LXRα is expressed primarily in liver, adipose tissue, intestine, macrophage, and kidney, whereas LXRβ is ubiquitous. In response to an increased concentration of cellular oxysterols, LXRs activate genes involved in "reverse cholesterol transport" from peripheral tissues to the liver and hepatic cholesterol metabolism.[66] LXRs induce the expression of proteins that stimulate cholesterol efflux from macrophages (ABCA1 and ABCG1), promote cholesterol transport in serum and uptake into liver (apolipoprotein E, phospholipid transfer protein, lipoprotein lipase, and cholesterol ester transfer protein), increase cholesterol catabolism into bile acids (CYP7A1), increase biliary secretion of cholesterol (ABCG5 and ABCG8), and inhibit absorption of cholesterol in the intestine (ABCG5, ABCG8, and ABCA1).[17,67-73] LXRs also increase the synthesis of fatty acids and triglycerides by up-regulating sterol regulatory element-binding protein 1c (SREBP-1c), the master regulator of fatty-acid synthesis.[74] Activation of LXR represses lipopolysaccharide induction of inflammatory mediators in macrophages, a mechanism with potential significance in atherosclerosis.[75]

Studies in animals have confirmed the physiologic role of LXRs as mediators of cholesterol metabolism and have suggested protective functions in the pathological contexts of atherosclerosis and hypercholesterolemia. In *Lxrα*-knockout mice, abnormal uptake and elimination of dietary cholesterol results in hepatic failure because of a profound accumulation of cholesterol esters.[72] High-affinity synthetic LXR agonists have been shown to increase hepatobiliary cholesterol secretion, decrease cholesterol absorption, and increase HDL levels in animal models.[17,76] In atherosclerosis-prone mouse models, LXR agonist treatment leads to increased HDL levels and decreased formation of atherogenic lesions.[77] Transplantation of bone marrow cells that are deficient in both LXRα and LXRβ into susceptible animals results in increased atherogenesis.[78] The propensity of LXR agonists to induce hepatic and serum hypertriglyceridemia, most likely via SREBP-1c up-regulation, is a potential barrier to the development of LXR agonists as cholesterol-lowering and antiatherogenic agents.[74,76]

Several approaches have the potential to lead to the development of selective LXR modulators that could decrease cholesterol accumulation and inhibit atherosclerosis without adversely affecting other serum lipid measures. For example, of the two LXR subtypes, LXRα is a more potent activator of SREBP-1c, suggesting that LXRβ-specific agonists might preferentially decrease cholesterol without causing substantial hypertriglyceridemia. Coactivator-specific LXR ligands might also have desirable effects on serum lipid profiles owing to distinct coactivator requirements at the SREBP-1c and ABCA1 promoters. Finally, certain derivatives of plant sterols, which are not absorbed but can activate LXR in enterocytes, would be expected to inhibit intestinal cholesterol absorption without inducing serum hypertriglyceridemia.[79] Creative attempts to maximize the therapeutic properties of LXR ligands are a promising example of the ap-

plication of biologic insight to receptor pharmacology.

FXR: BILE ACID SENSOR

Expressed in the enterohepatic system, kidney, and adrenals, FXR functions as a nuclear receptor for bile acids such as chenodeoxycholic acid and cholic acid.[80-82] FXR target genes regulate the secretion of bile acids and phospholipids into bile (bile salt efflux pump and multidrug-resistance proteins 2 and 3), the intestinal reabsorption of bile acid (ileal bile acid–binding protein), and hepatic cholesterol uptake from serum HDL (phospholipid transfer protein).[80,83-86] FXR indirectly mediates negative feedback repression of bile-acid synthesis by inducing a transcriptional repressor that decreases expression of CYP7A1, the rate-limiting enzyme in bile-acid synthesis.[87,88] FXR-deficient mice have increased serum levels of bile acids, total bile-acid pool size, and fecal bile-acid excretion — findings consistent with altered bile-acid homeostasis due to defective feedback inhibition of hepatic synthesis.[89] These defects lead to increased levels of serum total cholesterol, HDL, and triglycerides and to decreased HDL clearance.[90] Thus, it is perhaps not surprising that FXR agonists have a marked ability to reduce levels of hepatic and serum triglycerides and may be useful in treating hypertriglyceridemia.[91]

A recent finding suggests that FXR agonists may be effective in treating cholesterol gallstone disease, a condition that results from increased hydrophobicity of bile salts and supersaturation of biliary cholesterol.[86] Pharmacologic support for this idea comes from the finding that a potent synthetic FXR agonist can prevent all the sequelae of cholesterol gallstone disease in a murine model that mimics the human disease.[86] The clinical relevance of this finding may be particularly applicable in treating patients who have undergone cholecystectomy and are readmitted for recurring symptoms and acute pancreatitis associated with microlithiasis.

THYROID HORMONE RECEPTORS

The thyroid hormone receptors (TRs) are expressed throughout the body and regulate numerous metabolic functions such as lipid and carbohydrate metabolism, blood pressure, and body mass in response to thyroid hormone. Although TR activation could increase metabolism and promote weight loss, TR agonists have not been useful in the metabolic syndrome because of cardiac side effects and other adverse effects. Recent evidence, which suggests that TRα plays an important role in cardiac function and that TRβ preferentially regulates energy consumption and cholesterol metabolism, offers the possibility that isoform-specific TR agonists might safely increase energy expenditure.[92] To that end, a selective TRβ agonist has been demonstrated to reduce serum cholesterol, LDL, and body weight without increasing heart rate in primates.[93] Further studies will be required to determine if TRβ-specific activation can ameliorate aspects of the metabolic syndrome in humans.

PERSPECTIVES

The discovery cycle involving nuclear receptors has elucidated the molecular and physiological basis for a new class of pharmacophores that show promise for treating the metabolic syndrome. The availability of numerous approaches — including focused chemical-library screening, structure-based ligand design, and an enhanced understanding of nuclear-receptor regulation — should clearly aid this drug-discovery process. In addition, high-throughput efforts to catalogue nuclear-receptor expression and function, such as the Nuclear Receptor Signaling Atlas (www.nursa.org), are helping to establish a comprehensive database of the physiologic and pathologic features of nuclear-receptor systems. Given the disappointing number of new drugs being developed at most pharmaceutical companies, continued research into the RXR heterodimer discovery cycle for the improved treatment of the metabolic syndrome is a promising strategy whose time has come.

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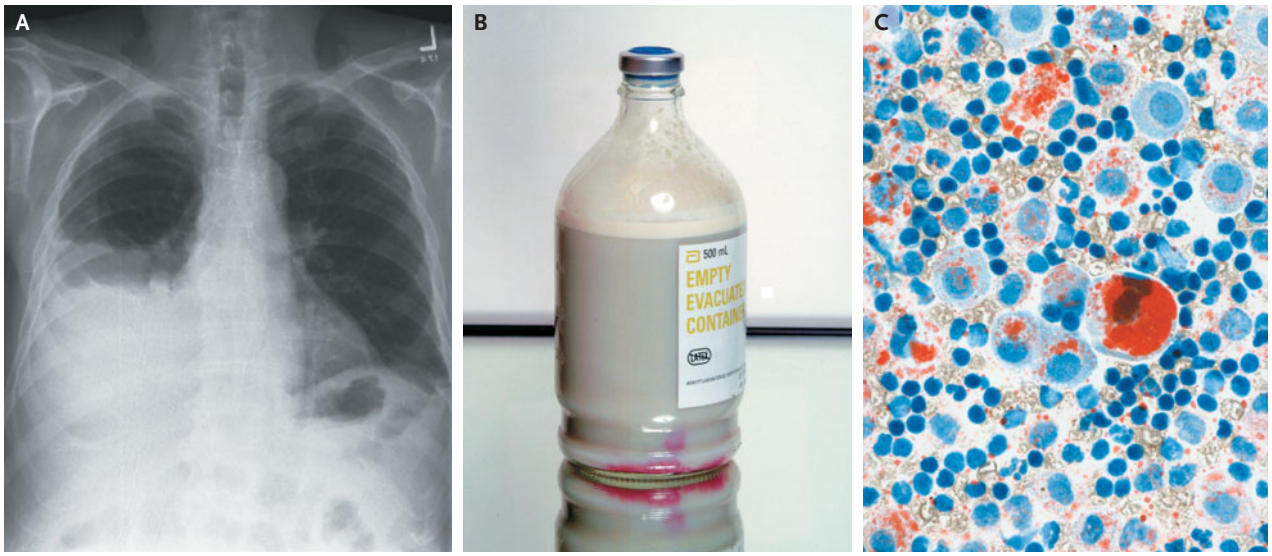
IMAGES IN CLINICAL MEDICINE

Chylothorax and Chyloperitoneum



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A 76-year-old man underwent elective repair of an abdominal aortic aneurysm, and in the subsequent eight weeks, exertional dyspnea, orthopnea, and abdominal pain developed. On physical examination, the patient was afebrile, and his vital signs were normal. There was a dull percussion note and decreased breath sounds over the right lower lung field. The abdomen was protuberant and diffusely tender. The serum triglyceride level was 1.21 mmol per liter (normal, <1.70 mmol per liter). A chest radiograph demonstrated a right pleural effusion (Panel A). Computed tomography of the abdomen revealed gross ascites containing particulate matter but no other abnormalities. Subsequent thoracentesis and paracentesis yielded a milky fluid (Panel B). Cytologic examination of the fluid by means of staining with oil red O showed lipid deposits within phagocytic cells (Panel C), leading to a diagnosis of chylothorax and chyloperitoneum. The pleural effusion and ascites resolved with drainage, adherence to a low-fat diet, and supplementation with medium-chain triglycerides (which directly enter the portal system rather than the intestinal lymphatics). The patient continues to do well at 18 months. It is presumed that the integrity of the thoracic duct was compromised during an otherwise uncomplicated repair of the aortic aneurysm.

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CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

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Case 24-2005: A 58-Year-Old Woman with Early-Stage Estrogen-Receptor–Positive Breast Cancer

Paula D. Ryan, M.D., Ph.D., Daniel B. Kopans, M.D., and Dennis C. Sgroi, M.D.

PRESENTATION OF CASE

A 58-year-old woman was seen in the multidisciplinary breast-cancer clinic of this hospital for management of early-stage breast cancer.

One month earlier, a routine screening mammogram at another facility revealed an ill-defined mass, approximately 15 to 20 mm in diameter, associated with calcifications in the lower inner quadrant of the right breast. The mass had not been present on a mammogram obtained two and a half years earlier. An ultrasonographic examination performed at this hospital 12 days after routine mammography showed a hypoechoic mass at the 3 o'clock position, measuring 1.2 cm in diameter. Two days later an ultrasonographically guided core biopsy was performed. Pathological examination of the specimen revealed invasive ductal carcinoma; as evaluated by immunohistochemistry, the tumor cells expressed amounts of both estrogen-receptor protein and progesterone-receptor protein; the expression of HER2/*neu* protein was 2+ out of 3+, but there was no amplification of the *HER2/neu* gene on fluorescence in situ hybridization (FISH). The patient chose to have breast-conserving therapy and was referred to the breast-cancer clinic.

Five years earlier, a papilloma had been excised from the patient's right breast, and 24 years earlier a fibroadenoma had been removed from her left breast. Menarche had occurred when she was 13 years of age; she was gravida 2, para 2, with a first pregnancy at the age of 27. She had used oral contraceptives in the past for four years. Menopause occurred at the age of 51, and she had never used hormone-replacement therapy. One year before the current evaluation, a computed tomographic (CT) scan of the abdomen that had been performed for evaluation of diverticulitis showed a left adnexal mass; left salpingo-oophorectomy was performed and revealed an ovarian fibroma. The patient had hypertension, hypercholesterolemia, hypothyroidism, and osteopenia. She was taking hydrochlorothiazide, atorvastatin, levothyroxine, a multivitamin, calcium, and vitamin D. A maternal aunt had received a diagnosis of breast cancer when she was in her 30s, and the patient's mother had died from a brain tumor at 39 years of age. Her father was alive and healthy at 84 years of age.

On physical examination, the patient appeared well, and her vital signs were normal.

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There was no lymphadenopathy. The lungs were clear, the heart sounds were normal, and the abdomen was soft with no masses or organomegaly. The breasts were symmetric with no suspicious nodularity in either breast, and there were no skin or nipple changes. There was no edema in her lower extremities. The results of a complete blood count and the levels of electrolytes, calcium, creatinine, urea nitrogen, protein, albumin, globulin, and bilirubin were all in the normal range.

Management options were discussed.

DIFFERENTIAL DIAGNOSIS

Dr. Paula D. Ryan: May we review the radiologic studies?

Dr. Daniel B. Kopans: The craniocaudal mammographic view (Fig. 1A) reveals an ill-defined mass with very small associated calcifications. In the mediolateral-oblique view, the lesion is in the inferior portion of the breast, close to the chest wall. These findings are also seen in the straight lateral view. Greater detail is seen in the magnified view. (Fig. 1A, inset). The fine, white specks are clustered calcifications; these are typically found in the intraductal portion of a cancer. There is an ill-defined mass associated with the calcifications in the lateral projection. These findings are highly suggestive of invasive ductal carcinoma with an intraductal component. The core biopsy confirmed the presence of an invasive ductal carcinoma.

Dr. Ryan: This postmenopausal patient presented with a small, nonpalpable breast cancer that was detected on mammography. The two issues in the management of early-stage breast cancer in a patient such as this are local control of the tumor in the breast and regional lymph nodes and systemic control of microscopic tumor that has already spread outside the breast.

A major decision that this patient faced was whether to undergo a mastectomy or to pursue breast-conserving therapy. Studies with 20-year follow-up have found that lumpectomy with irradiation is a safe and effective treatment for early-stage breast cancer.[1,2] This procedure coupled with sentinel-lymph-node biopsy has been determined to be a safe and accurate method of screening axillary lymph nodes for metastases in early-stage breast cancer, with an overall accuracy of 97 percent, sensitivity of 92 percent, and specificity of 100 percent.[3] Lumpectomy with sentinel-lymph-node mapping

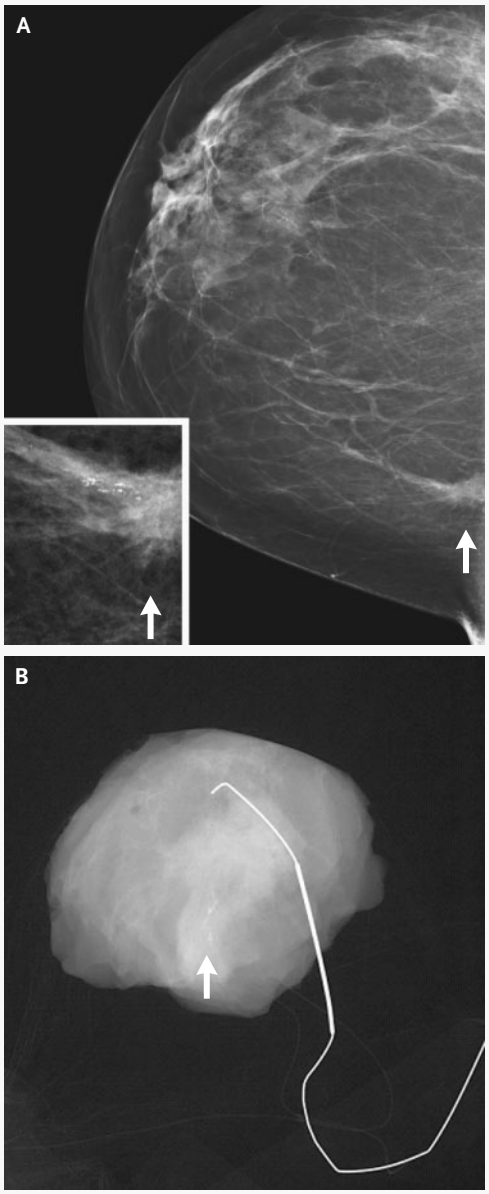

Figure 1. Radiologic Studies of the Breast and Lumpectomy Specimen.

The craniocaudal view from the mammogram reveals an ill-defined mass with very small associated calcifications in the inferior portion of the breast (Panel A), close to the chest wall (arrow). Magnification shows greater detail (Panel A, inset). The fine, white specks are clustered calcifications; these are typically found in the intraductal portion of a cancer. The radiograph of the specimen obtained by lumpectomy (Panel B) confirms the presence of both the microcalcifications and the tumor mass (arrow).

was offered to this patient; she chose this option rather than mastectomy.

This treatment is usually accompanied by systemic therapy with either hormones or their congeners or chemotherapy. Several pathological criteria are used to guide recommendations for systemic treatment of breast cancer. These include tumor size, tumor grade, the status of sentinel or axillary lymph nodes, and the presence or absence of the estrogen receptor, progesterone receptor, and *HER2/neu* gene amplification. The core biopsy revealed that this patient's tumor expressed both estrogen and progesterone receptors and did not have *HER2/neu* amplification. On the basis of this information, I considered hormonal therapy for her, but other factors, such as the tumor size, tumor grade, and status of the axillary lymph nodes, needed to be determined on the basis of evaluation of the lumpectomy specimen before a final recommendation for systemic treatment was possible.

PATHOLOGICAL DISCUSSION

Dr. Dennis C. Sgroi: When a lumpectomy is performed, the specimen is submitted for radiography before the pathological examination is performed. Dr. Kopans, may we see the specimen radiograph?

Dr. Kopans: As part of the lumpectomy procedure, needle localization was carried out. In cases such as this, in which the surgeon is unable to palpate the lesion, we place a guide wire to direct the surgeon to the lesion, using ultrasonographic, mammographic, or CT guidance. First, a needle is positioned into or alongside the lesion. The wire is then passed through the needle and into the desired location, so that it is stabilized in the tissue. The surgeon can then follow the wire down to the lesion and remove it.

The specimen radiograph (Fig. 1B) recapitulates what was seen on the mammogram. It shows an ill-defined mass that is consistent with an invasive cancer and the calcifications that presumably are in the in situ portion of this tumor.

Dr. Sgroi: Examination of the lumpectomy specimen from the right breast (Fig. 2A) revealed an invasive ductal carcinoma, 2.3 cm by 1.2 cm by 1.2 cm, that consisted of medium-sized, malignant epithelial cells infiltrating fibroadipose tissue as cohesive cords and nests, with no evidence of lymphatic vessel invasion. Associated with the invasive carcinoma was ductal carcinoma in situ harboring microcalcifications (Fig. 2B). The tumor was moderately differentiated (grade 2 of 3), with low-to-moderate mitotic activity. More than 60 percent of the tumor nuclei showed moderate-to-intense expression of both estrogen receptor and progesterone receptor,

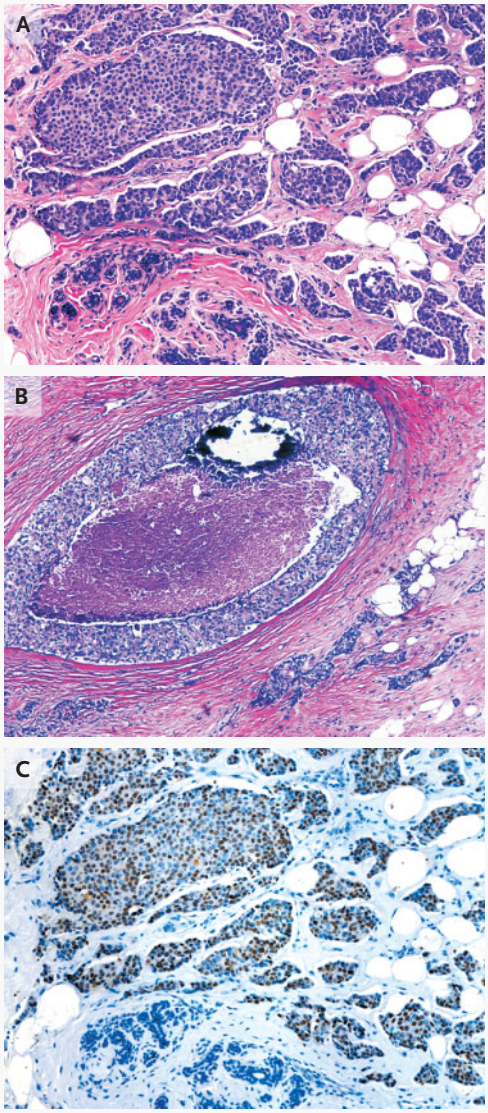

Figure 2. Histopathological Features of the Resected Breast Cancer.

A tissue section from the tumor, stained with hematoxylin and eosin, reveals nests and cords of malignant ductal epithelial cells invading fibroadipose tissue (Panel A) and associated ductal carcinoma in situ harboring microcalcifications (Panel B). The malignant ductal epithelial cells show nuclear expression of estrogen-receptor protein (Panel C, immunoperoxidase stain).

as determined by immunohistochemical staining (Fig. 2C). The tumor cells showed intermediate expression (2+ of 3+) of HER2/*neu* protein as determined by immunohistochemical analysis, but lacked *HER2/neu* gene amplification by FISH. The oncoprotein encoded by the *HER2/neu* oncogene is a member of the family of epidermal growth factor receptors called receptor tyrosine kinases. If there is either no protein expression or high-level expression, FISH is not needed. However, in cases such as this, with intermediate levels of protein expression, amplification must be confirmed or ruled out by FISH. A biopsy specimen of a sentinel node was negative for metastatic carcinoma.

The clinicopathological factors that are currently used for risk stratification often inaccurately predict the clinical course of breast cancer. Consequently, efforts are being made to identify new biomarkers that will assist providers in selecting optimal clinical-management strategies for a patient such as the one in this case. Gene-expression–profile analysis with DNA microarrays is used in the classification of human cancers because it provides a comprehensive molecular analysis of genes expressed by the tumors. In microarray analysis, nucleic acid polymer probes are immobilized on a solid surface; fluorescent-labeled RNA from tumor samples is then layered on the microarray, and RNA molecules bind to complementary gene sequences. Thousands of genes from human tumor samples can be assessed simultaneously, making it possible to detect differential gene-expression patterns, or signatures, that distinguish them from normal tissues, other types of tumors, and tumors with a different prognosis or response to treatment.

Studies of gene-expression profiles based on microarray analysis in breast cancers have shown that morphologically similar cancers in different patients can be made up of distinct subtypes when analyzed at the molecular level.[4-7] Furthermore,[6,8] the pattern of genes expressed in these specific subtypes of cancer is likely to be representative of the molecular pathways driving malignant transformation. Recent studies linking gene-expression profiles to clinical outcome have shown that the potential for distant metastasis and the probability of overall survival can be predicted on the basis of the biologic characteristics of the primary breast tumor.[9] Several retrospective studies of breast cancer have shown that analysis of gene-expression profiles can identify prognostic categories that may guide treatment choices more effectively than available clinicopathological prognostic tools.[10-14]

Three studies in which distinct methods were used have suggested that gene-expression analysis may be useful in identifying prognostic markers for breast cancer. In one study,[10] a 70-gene signature assessed by microarray analysis effectively stratified a large group of premenopausal patients with stage I or II breast cancer into a subgroup of patients with a good prognosis and a subgroup with a poor prognosis. Two studies[13,15,16] addressed the use of gene-expression analysis to predict recurrence of lymph-node–negative breast cancer that had been treated with tamoxifen. In one study, the expression ratio of two genes, assessed with the use of reverse-transcriptase–quantitative polymerase-chain-reaction (RT-QPCR) analysis of paraffin-embedded tissue, predicted the likelihood of recurrence in a small cohort of patients with node-negative breast cancer treated with tamoxifen alone.[13,15,16] Another study[14] analyzed a set of 21 genes, using RT-QPCR on paraffin-embedded tissue to generate a "recurrence score," which effectively predicted which patients would remain free from distant recurrence. Although these gene-expression signatures or recurrence scores may not be completely independent of tumor grade, they lack the subjectivity and interobserver variability associated with current tumor-grading classification schemes. The 21-gene signature test is commercially available.

DISCUSSION OF MANAGEMENT

Dr. Ryan: As summarized by Dr. Sgroi, this patient had a breast cancer of pathological stage T2N0, according to the American Joint Committee on Cancer staging criteria for breast cancer, with a tumor size of 2.3 cm, grade II, and no tumor identified in the sentinel lymph node. The tumor cells were positive for estrogen and progesterone receptors, and negative for *HER2/neu* amplification. At this point, we needed to decide on the optimal systemic therapy for this patient.

Adjuvant tamoxifen therapy in a postmenopausal woman with estrogen-receptor–positive breast cancer provides an annual reduction in the chance of death from breast cancer of 31 percent, whereas chemotherapy provides a 20 percent reduction.[17] In a postmenopausal patient such as this with breast cancer that is node-negative and with a baseline risk of recurrence that is low, the benefit of adding

systemic chemotherapy may be quite small, especially after factoring in the toxicity of chemotherapy as compared with tamoxifen.

There are published guidelines from the National Institutes of Health (NIH) and the St. Gallen consensus conferences on the adjuvant treatment of early-stage breast cancer that can help clinicians in their recommendations for chemotherapy, but these guidelines differ in whether chemotherapy is recommended or not, depending on the size of the tumor and other histopathological criteria.[18,19] With the use of the 70-gene prognosis signature described by Dr. Sgroi, the high-risk groups defined by either the NIH or the St. Gallen criteria included some patients who had a good-prognosis signature, and conversely, the low-risk groups identified by these criteria included some patients with a poor-prognosis signature.[11]

The patient in this case had a tumor with predominantly good prognostic features with the exception of the size. According to the NIH criteria, for a tumor size of 2.3 cm, chemotherapy would be recommended, in addition to tamoxifen. Chemotherapy, however, would provide a very small additional benefit in this case. For example, on the basis of estimates by Adjuvant! (www.adjuvantonline.com),[20] a computerized model that calculates the risk of recurrence and death in women with invasive breast cancer with and without adjuvant systemic therapy, chemotherapy would provide an additional benefit of 3.4 percentage points as compared with tamoxifen alone for recurrence and a 1.2 percentage point improvement in survival at 10 years.[20] This case is an example of one in which novel biomarkers that predict clinical outcome would assist in the decision about whether to recommend hormonal therapy alone or with chemotherapy.

Finally, for patients for whom hormonal treatment is recommended, an aromatase inhibitor is another option. The Arimidex, Tamoxifen, Alone or in Combination Trial found an absolute benefit in terms of overall disease-free survival of the aromatase inhibitor anastrozole over tamoxifen of 2.4 percent at four years among postmenopausal women with invasive breast cancer in a randomized trial of these drugs given immediately after surgical treatment.[21] The Intergroup Exemestane Study assigned postmenopausal patients after two to three years of tamoxifen therapy at random either to complete five years of therapy with tamoxifen or to receive exemestane to complete the five years. The hazard ratio for disease-free survival was 0.68 ($P<0.001$) in favor of exemestane therapy.[22] Among women who had completed at least five years of adjuvant tamoxifen therapy, letrozole was associated with an improved disease-free survival rate at four years (93 percent) as compared with placebo (87 percent).[23]

With these data, a recent technology assessment from the American Society of Clinical Oncologists suggested that adjuvant therapy for postmenopausal women with hormone-receptor–positive breast cancer should include an aromatase inhibitor.[24] What remains to be clarified is the appropriate sequence, timing, and duration of adjuvant hormonal therapy. An interesting question is whether novel biomarkers identified by molecular profiling of tumors will also help guide our decision making with respect to hormonal therapy. If we can determine and validate a biomarker for tamoxifen resistance, then specific patients may be more appropriate candidates to receive an aromatase inhibitor at their initial diagnosis.

The patient under discussion recovered well from lumpectomy and sentinel-lymph-node biopsy. After a discussion regarding the benefit of chemotherapy as compared with endocrine therapy alone, the decision was made to proceed with treatment with anastrozole alone. The patient received adjuvant radiation therapy and is presently doing well, one year after she received the diagnosis of breast cancer.

ANATOMICAL DIAGNOSIS

Invasive ductal carcinoma, T2N0, positive for estrogen receptor and progesterone receptor, negative for *HER2/neu* amplification.

Dr. Sgroi reports that he is a named coinventor on a pending patent application to use the HOXB13:IL17BR expression ratio to ascertain breast-cancer prognosis. The technology is co-owned by Massachusetts General Hospital and Arcturus Bioscience; Massachusetts General Hospital has licensed its rights in the patent to Arcturus.

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EDITORIAL

Combination and Sequential Therapy for Osteoporosis

Robert P. Heaney, M.D., and Robert R. Recker, M.D.

For an investment approaching $1 billion, a pharmaceutical manufacturer may obtain approval from regulatory agencies to market a specific dose of a given medication for the treatment or prevention of a particular disorder. Such approval emphasizes and is based largely on the demonstration of simple efficacy and safety. Often little is known, not just about unanticipated side effects of the drug, much in the news of late, but also about such fundamental and critically important issues as the optimal duration of treatment; the effects, if any, of interactions with other agents affecting the same organs or tissues; or optimal sequencing of the various available treatments. These questions are important to practitioners whose patients have the particular disease but who rarely have it in the pristine, often untreated form encountered in patients participating in clinical trials.[1] Providing answers to these questions is often left to the less structured world of clinical practice and to formal testing of ad hoc combinations and sequences.

Over the past 10 years, five agents have been approved for the treatment or prevention of osteoporosis in the United States. As a group, these drugs have revolutionized the management of osteoporosis. They fall into two broad categories — agents that reduce the often exaggerated bone remodeling in postmenopausal women (and patients with osteoporosis, generally)[2] and those that stimulate bone formation. Agents exhibiting each mode of action have been shown to reduce the risk of fracture substantially (i.e., both classes of agents are efficacious). However, it has been uncertain whether such drugs enhance each other's effects if given together or in certain sequences or whether one agent alters responsiveness to the other.

Two articles in this issue of the *Journal*, one by Black et al.[3] and one by Cosman et al.,[4] provide important, if still incomplete, information about the effects of sequences and combinations of so-called bone-active agents in current clinical practice. The conclusions one can draw are preliminary, in part because not all relevant questions have been addressed and in part because these newer studies, which involve small numbers of patients, are unable to assess the relative antifracture efficacy of the various combinations likely to be encountered in practice.

Confining attention solely to effects on bone mass, one can state with reasonable certainty that the bisphosphonates produce a steady increase in bone mineral mass that, although not linear, averages about 1 percent per year for up to 8 to 10 years. Once-daily parathyroid hormone, administered as either the 1–34 or the 1–84 amino acid form of the molecule, increases central bone mass to a substantially greater extent (8 to 10 percent per year for up to two years of treatment, the period for which data are available). Using these figures as rough benchmarks, the findings from these two studies,[3,4] together with those of other studies they cite, allow one to draw a number of conclusions.

First, both classes of agents appear to be efficacious as monotherapy. Second, combination therapy with parathyroid hormone and a bisphosphonate appears to increase central bone mass, but to a lesser extent than does parathyroid hormone alone. Third, in the months and years after treatment with parathyroid hormone, some or all of the bone gained during treatment appears to be lost if no further therapy is implemented. Fourth, administering bisphosphonates after a course of parathyroid hormone appears to conserve the bone gained during therapy with parathyroid hormone and adds a further quantum of bone in its own right, roughly similar in magnitude to the short-term effect of

bisphosphonates given to previously untreated patients. Finally, parathyroid hormone appears to retain its anabolic effect in patients previously treated with a bisphosphonate, although the effect is probably smaller than that seen in previously untreated patients.

We would stress that these conclusions reflect the effects of the drug on bone mass alone. We note that there are strong reasons to conclude that the antifracture efficacy of both classes of agents derives, in part, from effects distinct from mass changes and that these effects may be at least as important in determining their antifracture efficacy as their effects on bone mass. For example, in addition to producing a small increase in bone mass, bisphosphonates and the other antiresorptive agents also promptly reduce the number of active remodeling loci on bone surfaces. These loci are believed to concentrate mechanical stress in adjacent bone when the structure bears weight, and a reduction in their number produces a prompt decrease in bone fragility, independent of any effect on bone mass.[5] Furthermore, in addition to increasing trabecular bone volume, parathyroid hormone also increases the periosteal diameter at critical bony sites.[6] Other things being equal, the latter effect increases the cross-sectional moment of inertia and improves bony resistance to bending.

These features of osteoporosis and its response to treatment are not related to bone mass and are often grouped under the catchall phrase "bone quality." Defects in "quality" probably equal or even outweigh the mass defect in bone implied in the name for this condition, "osteoporosis." Thus, although the effect of combined treatment with a bisphosphonate and parathyroid hormone on bone mass seems to be less than that produced by treatment with parathyroid hormone alone, it could be that the antifracture efficacy of the combination is additive. This would be the case, for example, if it turns out that the bisphosphonate's effect on remodeling and the effect of parathyroid hormone on periosteal bone formation are each sufficiently expressed. Only time (and much larger studies) will provide answers to such questions.

Given the heterogeneity of osteoporosis, it is unlikely that all patients will have an equally good response to all drugs in either class. "What is the treatment of choice for my patient?" remains an important question, particularly since treatment with parathyroid hormone (1–34) is limited by approved indications to a two-year period. Established efficacy data apply to groups of patients, not necessarily to individual patients, some of whom may appear to have no response to treatment with a particular regimen. Indeed, the delineation of such so-called treatment failure is a complicated and still unresolved issue. However, in the world of clinical practice, apparent failure often leads to a change in medication and is a major driver of the sequences discussed here. Although some of the issues involved in the sequential use of these drugs have been addressed by Black et al. and Cosman et al., other therapeutically important questions remain. For example, should patients with low initial rates of bone remodeling[2] receive a suppressor of bone remodeling, or would they be better served by treatment with parathyroid hormone from the outset?

We need the current and expanding variety of treatments for osteoporosis precisely because it is a multifactorial disorder, unlikely to be controlled in all patients by any single class of medication. The good news is that an expanding array of potent, generally well tolerated bone-active agents that operate through a variety of mechanisms have been developed and that more promising drugs are on the horizon.

Dr. Heaney reports having received consulting fees from Merck and Lilly.

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CORRESPONDENCE

Rickettsia parkeri Infection and Other Spotted Fevers in the United States

TO THE EDITOR: Extensive cross-reactivity exists among antigens of various spotted-fever–group rickettsiae, and routine serologic assays are generally insufficient to identify conclusively the specific rickettsial agent responsible for the infection. Since 1989 one of us (Dr. Raoult) has investigated the reactivity of serum specimens from patients with various rickettsioses to define the serologic criteria for several of these infections in the Eastern Hemisphere.[1,2] *Rickettsia parkeri*, a spotted-fever–group rickettsia first identified in 1939 in Gulf Coast ticks (*Amblyomma maculatum*) collected from Texas, has only recently been shown to be a cause of the disease in the United States.[3] Herein we describe the use of Western blot techniques to show that additional human cases of infection with *R. parkeri*, or possibly other unrecognized spotted-fever–group rickettsiae, may have occurred in the United States.

Serum specimens from patients in the United States with rickettsioses are routinely submitted to the Centers for Disease Control and Prevention for diagnostic testing. Aliquots of 15 specimens with antibodies reactive with *R. rickettsii*, the agent of Rocky Mountain spotted fever, were evaluated at the Unité des Rickettsies, in Marseille, France, with the use of microimmunofluorescence and Western blot assays that compare the responses of antibodies against antigens of *R. rickettsii* and *R. parkeri*. Microimmunofluorescence assays showed that four patients had higher titers (by at least two dilutions) of IgG and IgM antibody to *R. rickettsii*, and five patients had higher titers of antibody to *R. parkeri*, and in six patients no difference between titers was observed. Four serum specimens with titers of antibody to *R. parkeri* that were greater than or equal to those to *R. rickettsii* on microimmunofluorescence assay were available in sufficient quantity to evaluate with the use of Western blot analysis, and each reacted with a 120-kD protein of *R. parkeri* (Fig. 1), a finding suggestive of infection with this agent.

These preliminary data are limited by the lack of accompanying clinical or epidemiologic correlates; however, the findings suggest that some infections with *R. parkeri* were previously classified as Rocky Mountain spotted fever. Recognized or potential arthropod-borne spotted-fever–group rickettsial pathogens in the United States, other than *R. rickettsii*, include *R. akari*, *R. felis*, *R. parkeri*, *R. amblyommii*, *R. rhipicephali*, and various unnamed serotypes (e.g., Tillamook and 364-D).[4,5] Further molecular and culture-based studies will be needed to differentiate definitively the serologic responses of patients to these various agents. Nonetheless, the coexistence of several rickettsioses caused by distinct spotted-fever–group rickettsiae, increasingly recognized in Europe, Africa, and Asia, may also occur in the Western Hemisphere, and it is possible that several species of rickettsia, including *R. parkeri*, are responsible for cases of tick-borne rickettsiosis that have been described in the United States during the past century.

THIS WEEK'S LETTERS

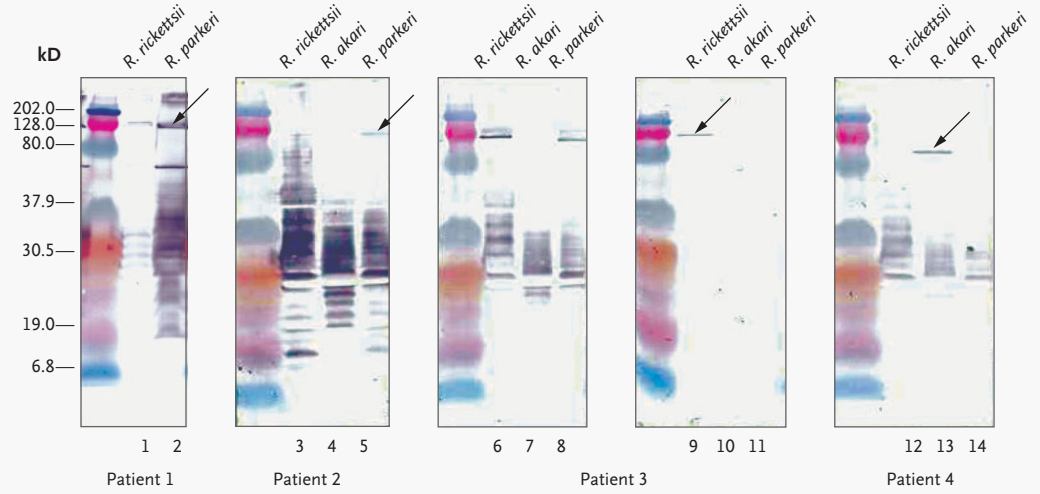

Figure 1. Results of Western Blot Assay of Serum from Four Patients in the United States with Various Confirmed or Suspected Spotted-Fever Rickettsioses.

The assays reacted with antigens of *R. rickettsii*, *R. parkeri*, or *R. akari*. Rocky Mountain spotted fever was suspected in Patient 1 (lanes 1 and 2). Patient 2 (lanes 3, 4, and 5) had polymerase-chain-reaction (PCR)–proved and culture-proved *R. parkeri* rickettsiosis. The results of the assay from Patient 3, who had PCR-proved Rocky Mountain spotted fever, are shown before (lanes 6, 7, and 8) and after (lanes 9, 10, and 11) adsorption with *R. parkeri* antigen. Patient 4 had PCR- and culture-proved rickettsialpox (lanes 12, 13, and 14). Reactivity with a 120-kD protein of *R. parkeri* is seen in the specimens from Patient 1 (arrow, lane 2) and from Patient 2 (arrow, lane 5). Reactivity with high-molecular-weight proteins of *R. rickettsii* and *R. parkeri* is seen in the specimen from Patient 3 (lanes 6 and 8); after adsorption with *R. parkeri* antigen, only reactivity with *R. rickettsii* remains (arrow, lane 9). No reactivity with *R. rickettsii* or *R. parkeri* was present after adsorption with *R. rickettsii* antigen (data not shown). Reactivity with a 90-kD protein of *R. akari* is seen only in the serum of Patient 4, who was infected with *R. akari* (arrow, lane 13).

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Amiodarone versus Sotalol for Atrial Fibrillation

TO THE EDITOR: Singh et al. (May 5 issue)[1] report in their article that both amiodarone and sotalol are efficacious in improving quality of life and sustaining sinus rhythm in patients with atrial fibrillation. They also report, but dismiss as statistically insignificant, a higher incidence of death in both groups of patients as compared with the placebo group.

On the basis of their data, the absolute increase in the risk of death in the amiodarone and the sotalol groups, as compared with the placebo group, was 2.7 and 3.6 percentage points, respectively, with a

number needed to harm of between 27 and 37. In light of the prevalence of atrial fibrillation, these numbers are potentially important and merit further attention. The authors state that this difference is "unlikely" to be of practical significance on the basis of the results of larger studies with these drugs. This conclusion is potentially misleading, since the cited articles are mostly not studies conducted in patients with atrial fibrillation, there was limited follow-up, and in only one study was there a placebo group.[2-4] This potential finding should be kept in mind when deciding on optimal patient care and designing future studies.

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TO THE EDITOR: In the study by Singh et al., patients received antiarrhythmic drugs while they had atrial fibrillation and underwent conversion to sinus rhythm if atrial fibrillation persisted on the 28th day of the study. There were eight sudden deaths and one documented episode of torsades de pointes in the sotalol group. Although there are ample data to support the outpatient initiation of amiodarone during atrial fibrillation,[1] conversion to sinus rhythm is associated with an increased risk of torsades de pointes, particularly in the presence of quinidine.[2] In the Sotalol Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T), the authors suggest that outpatient initiation of sotalol during atrial fibrillation may be appropriate. The study population comprised more than 98 percent men. The incidence of drug-induced torsades de pointes is lower among men than among women, and this difference may explain the low rates of proarrhythmia in this trial.[3] We believe that caution should be exercised in generalizing the practice of outpatient loading of sotalol during ongoing atrial fibrillation, particularly with regard to women.

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TO THE EDITOR: Singh et al. administered "thyroid-function tests" at enrollment but did not report the incidence of thyroid dysfunction during their 4.5-year trial. This is puzzling, given the very high reported incidence of both hypothyroidism and hyperthyroidism in various observational, cross-sectional, and controlled trials involving amiodarone for the treatment of several types of arrhythmia.[1] Whereas amiodarone-induced hypothyroidism is readily treated with levothyroxine, amiodarone-induced hyperthyroidism is quite challenging to treat, particularly in patients who already have underlying atrial fibrillation and in those in whom amiodarone may not be stopped. Radiofrequency ablation is not an option, because of the massive iodine load of each dose of amiodarone, and surgery is not always an option for patients with severe coronary artery disease. Finally, potentially toxic therapies, such as glucocorticoids or potassium perchlorate, are used in some instances. Similar questions may be posed about the one-year Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) substudy of the first antiarrhythmic drug in serial therapy.[2]

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1. Newman CM, Price A, Davies DW, Gray TA, Weetman AP. Amiodarone and the thyroid: a practical guide to the management of thyroid dysfunction induced by amiodarone therapy. Heart 1998;79:121-7.
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TO THE EDITOR: Singh et al. report no significant difference between the groups who received amioda-

rone or sotalol and the placebo group in terms of major adverse effects. However, because their study was limited to a maximum follow-up of 4.5 years, the far-reaching adverse effects of amiodarone — namely, pulmonary and hepatic toxic effects, which can occur long after a period of this length — must also be examined and weighed when deciding between the two drugs. More than half of patients receiving long-term amiodarone therapy eventually discontinue its use because of such adverse effects. Extending this study over a longer interval might be helpful in establishing comparative side-effect profiles. In addition, it may be prudent to take into consideration the many other cardiac medications often taken by patients with atrial fibrillation, including digoxin and warfarin, which may also adversely interact with amiodarone, when the choice is made between this therapy and sotalol.

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THE AUTHORS REPLY: Dr. Rubinstein expresses concern that we misinterpreted differences in mortality in the SAFE-T. However, trials assessing mortality are typically much larger than SAFE-T, and extrapolating our data may be unreliable. Also, there was an uneven distribution of patients with hypertension (73 percent in the amiodarone group, 66 percent in the sotalol group, and 56 percent in the placebo group; P=0.004). In an atrial-fibrillation study[1] similar to SAFE-T but without a placebo control, there were nine deaths among the 201 patients assigned to amiodarone and a total of eight among the 101 patients assigned to sotalol and the 101 assigned to propafenone. Death due solely to atrial fibrillation may be relatively rare and in the study population may be due largely to associated cardiovascular disorders.[1] This is suggested by the deaths in the placebo group in SAFE-T. Moreover, a meta-analysis[2] of 13 trials (involving 6500 patients) showed a 13 percent reduction in total mortality with amiodarone as compared with controls (P=0.03).

In response to Drs. Zimetbaum and Josephson, we found no valid data supporting in-hospital initiation of sotalol or an increased incidence of torsades de pointes among women with atrial fibrillation. Recent evidence suggests that QT intervals in postmenopausal women are similar to those in men. In SAFE-T, the single case of torsades de pointes (nonfatal) occurred at eight weeks. Drs. Zimetbaum and Josephson emphasize that quinidine-induced torsades de pointes usually occurs during conversion to sinus rhythm. In SAFE-T, spontaneous conversion occurred fully three weeks after drug initiation and without torsades de pointes (in 27 percent of the patients in the amiodarone group and 24 percent in the sotalol group). Available data suggest that the safety of sotalol depends critically on limiting creatinine clearance to more than 60 ml per minute and the QT interval to less than 550 msec and not on initiating in-hospital therapy.

In response to Dr. Desai, in SAFE-T, with the use of low drug doses, the rates of adverse events and withdrawal were very low. In another study,[3] the incidence of pulmonary toxic effects was 1.1 percent among 269 patients receiving amiodarone — an incidence similar to that (0.8 percent) among the 250 patients receiving placebo. A meta-analysis involving 1465 patients in low-dose, placebo-controlled trials reported a significant decrease in the odds of pulmonary toxic effects.[4] The data suggest that pulmonary toxic effects in patients receiving amiodarone may occur more as a function of dose than of duration of therapy. We agree with Dr. Desai that long-term data on pulmonary toxic effects would be of considerable importance to the clinical use of amiodarone. Surprisingly, however, Dr. Desai considers hepatic toxicity a "far-reaching adverse effect" of amiodarone. Levels of liver enzymes increase during amiodarone-loading therapy but normalize during maintenance therapy. Serious persistent hepatotoxicity is rare[5] and is usually associated with preexisting liver disease.

In response to Dr. Schlegel, thyroid function was assessed and an analysis of the data is under way.

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Multidetector-Row Computed Tomography in Suspected Pulmonary Embolism

TO THE EDITOR: Complex diagnostic algorithms are in vogue for the diagnosis of venous thromboembolism. In yet another management study, Perrier et al. (April 28 issue)[1] propose a combination of multislice computed tomography (CT) and D-dimer measurement as a strategy to diagnose pulmonary embolism, as discussed in an editorial by Goldhaber.[2]

I am uncomfortable with the suggestion that a strategy that results in a 1-in-50 risk of pulmonary embolism at follow-up is hailed as a breakthrough.

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TO THE EDITOR: Perrier et al. show that among patients who had multidetector CT scans showing no pulmonary embolism, only 0.9 percent were found to have proximal deep venous thrombosis on ultrasonography. On the basis of these results, the authors suggest that future studies be done to determine whether ultrasonography can be safely eliminated from the diagnostic workup of patients with a negative CT scan. Pending a true cost-effectiveness analysis, however, I wonder how many physicians would be comfortable missing even 0.9 percent of cases of deep-vein thrombosis, considering the life-threatening potential of untreated venous thromboembolism. I also wonder whether the authors would have been comfortable forgoing therapy in the three patients who had a negative CT and then received a diagnosis of deep venous thrombosis. If their answer is yes, then perhaps the study they suggest is warranted.

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THE AUTHORS REPLY: We thank Dr. Turpie and Dr. Siegel for their interest in our work. Both express concern about the rate of false negative results associated with our diagnostic strategy. The overall failure rate of our algorithm was 1.5 percent. This rate included the thromboembolic events that would have been missed if ultrasonography had not been included in the initial workup and the thromboembolic events during the three-month follow-up period among patients in whom pulmonary embolism had been ruled out and, therefore, had not been treated. This 1.5 percent risk of thromboembolic events is similar to the risk among patients who were left untreated on the basis of a negative pulmonary angiogram and might reflect recurrence of an initially undetected thromboembolic event or the occurrence of a new, unrelated event in patients with continuing risk factors for venous thromboembolism.

Dr. Turpie judges our strategy to be complex. In fact, we believe our results allow a simplification of existing strategies, since they suggest that a negative result on venous-compression ultrasonography of the lower limbs is no longer required to rule out pulmonary embolism in a patient with a negative multidetector CT scan. However, Dr. Siegel is uncomfortable with that simplification because of the 0.9 percent risk of missing an acute venous thromboembolic event if lower-limb ultrasonography is not performed. Again, that risk was included in the 1.5 percent overall failure rate of a diagnostic strategy that did not include ultrasonography. We agree that a formal cost-effectiveness analysis should be performed, but it is difficult to imagine that a strategy requiring more than 100 ultrasonographic studies to pick up one additional deep venous thrombosis would be cost-effective. Moreover, ultrasonography also has its limitations, and at least some of the deep-vein thromboses detected by systematic examination of patients who had thoracic symptoms but no lower-limb symptoms might be false positives, caused by absence of recanalization of a previous clot.

CORRECTION

Amiodarone versus Sotalol for Atrial Fibrillation

Amiodarone versus Sotalol for Atrial Fibrillation . On page 628, in the letter by Schlegel, lines 14 and 15 should have read, ``Radio-ablation is not an option . . .,´´ rather than ``Radiofrequency ablation is not an option . . .,´´ as printed. We regret the error.

N Engl J Med 2005;353:1869-b

In summary, no single test or strategy allows the detection of all pulmonary emboli. The discomfort expressed by the commentators should probably be attributed to the difficulties inherent in the diagnosis of pulmonary embolism rather than to our diagnostic scheme.

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THE EDITORIALIST REPLIES: Dr. Turpie overlooks some key points. The diagnostic algorithm presented by Perrier et al. is simple, not complex. Clinical likelihood assessment (which can be done by "gestalt") and D-dimer enzyme-linked immunosorbent assays can quickly rule out pulmonary embolism in many patients who otherwise would needlessly undergo imaging. This approach is reliable and cost-effective.

The 1-in-50 risk of pulmonary embolism after three months of follow-up with chest CT scanning as the principal imaging test matches the follow-up results obtained with the invasive alternative: classic pulmonary angiography, which increases discomfort, risk, and cost.[1]

With respect to multislice chest CT,[2] this approach has led to four changes in diagnostic approach: venous ultrasonography of the legs is no longer necessary when multislice chest CT scanning rules out pulmonary embolism; the size and accessibility during surgery or catheterization of the pulmonary embolism can be immediately ascertained; detection of right ventricular enlargement identifies high-risk patients with ominous prognoses[3]; and if pulmonary embolism is ruled out, chest CT may detect alternative diagnoses that explain the presenting symptoms and signs.

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Detection of Acute HIV Infections

TO THE EDITOR: The recent article by Pilcher et al. (May 5 issue)[1] described successful public health methods to control HIV transmission, but the authors' findings may not be generalizable to states that do not have confidential HIV-reporting systems, such as California. In the fall of 2003, we initiated a program of RNA screening, routine patient interviewing, and HIV genotypic-resistance testing at the San Francisco municipal sexually transmitted disease (STD) clinic.

During 2004, we identified 136 of 3789 persons (3.6 percent) as having an HIV infection, among them 11 (0.3 percent) who had an acute infection. HIV RNA screening increased the rate of HIV case detection to 8.8 percent, more than double the overall rate of 3.9 percent reported by Pilcher et al. Eight percent of the viruses detected exhibited drug resistance to one drug class, 4 percent to two drug classes, and none to more than two drug classes. Interviews with patients elicited information about 112 sex partners, 10 of whom were newly identified as having an HIV infection.

The combined data support the real benefit that routine HIV RNA screening, HIV resistance surveillance, and patient interviews can have in the control of HIV. Further efforts should be made to strengthen and expand HIV-control efforts in STD clinics as well as to ensure confidential HIV reporting nationwide.

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1. Pilcher CD, Fiscus SA, Nguyen TQ, et al. Detection of acute infections during HIV testing in North Carolina. N Engl J Med 2005; 352:1873-83.

TO THE EDITOR: Pilcher and colleagues added nucleic acid amplification to diagnose HIV infection in a cohort of 109,250 persons. They concluded that "this form of testing should be a standard tool for the prevention and surveillance of HIV infection." However, HIV experts[1,2] and the maker[3] of the RNA test used by the authors assert that it "is not to be used as a screening test for blood or blood products for HIV or as a diagnostic test to confirm the presence of HIV infection." The Centers for Disease Control and Prevention (CDC)[4] asserts that "in adults, adolescents, and children infected by other than perinatal exposure, plasma viral RNA nucleic acid tests should not be used in lieu of licensed HIV screening tests."

The confirmatory Western blot test used by the authors was considered positive according to the revised CDC criteria. However, the criteria for a positive Western blot remain unstandarized. Band patterns considered proof of HIV infection vary among laboratories, institutions, and countries (Table 1).[5] For example, results that are positive according to the revised CDC criteria are not considered positive by the Food and Drug Administration or by the National Serology Reference Laboratory in Australia. Thus, a situation may arise wherein a person considered seropositive and infected according to one set of criteria may be serologically indeterminate and not infected according to another, and vice versa.

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THE AUTHORS REPLY: Dr. Turner notes correctly that HIV nucleic acid amplification tests are not marketed for clinical diagnostic use. Generally, this is understandable: the specificity of nucleic acid amplification tests can be as low as 97 percent — inadequate for HIV screening, except in clinical circumstances in which the pretest probability of infection is extremely high (for instance, in the evaluation of suspected acute retroviral syndromes). However, group-testing algorithms in our study drastically cut the number of individual samples tested by nu-

Table 1. Global Variation in the Criteria for a Positive Western Blot.*

Organization	Criteria
CDC and ASTPHLD	Two bands of GP41 or GP120/GP160 or p24
FDA (United States)	p24 and p31 and either GP41 or GP120/GP160
SFTS (France)	
Unequivocally positive	Two ENV bands (GP160 and GP120) with GAG or POL
Probably positive	ENV (GP160) and GAG (p24)
Probably positive	Two ENV bands only (GP160 and GP120)
World Health Organization	Two ENV bands, with or without GAG or POL
CRSS and Pan American Health Organization	One p24 or p31 band and one ENV band
American Red Cross	One GAG band, one POL band, and one ENV band
Paul Ehrlich Institut (Germany)	Two bands; one must be ENV
China	Two ENV bands or one ENV band and p24
Singapore	Two ENV bands (GP160/GP41 and GP120) and any GAG or POL band
Australia	One ENV band and any three GAG or POL bands

* CDC denotes Centers for Disease Control and Prevention, ASTPHLD Association of State and Territorial Public Health Laboratory Directors, GP glycoprotein, FDA Food and Drug Administration, SFTS Sanguine Nationale Transfusion Sociétés, and CRSS Consortium for Retrovirus Serology Standardization. Data are from Genelabs.[5]

cleic acid amplification, resulting in excellent specificity (>99.99 percent) for the combined antibody and nucleic acid amplification approach. The positive predictive value for positive results on nucleic acid amplification testing among antibody-negative clients was remarkably high (90 percent), considering the low prevalence of the disease. It is interesting to note that nucleic acid amplification tests are both licensed and marketed for diagnostic testing of blood donors, for which the group-testing strategy is preferred. Still, even when pooled, nucleic acid amplification tests must be considered screening tests that, if positive, warrant additional testing to confirm or rule out seroconversion. With regard to our study's criteria for HIV-antibody positivity on confirmatory testing, varying Western blot criteria made no difference in the results. Moreover, the various Western blot criteria have very little or no effect on the sensitivity of antibody screening (the problem with current antibody testing that the addition of nucleic acid amplification testing aims to improve).

Dr. Klausner and colleagues point to the fact that the public health infrastructure in North Carolina favored the state's success in implementing testing procedures for acute HIV infection. In addition to confidential testing, the state also has invested in the systems necessary for partner counseling and referral, with staffing by specialists experienced in HIV and STD intervention, and continues to favor the use of venipuncture (as opposed to oral-fluid or finger-prick–blood collection) at most HIV-testing sites. Particularly in areas with a high burden of HIV disease, such as California, the potential benefit of programs designed for the prevention of acute HIV infection may merit reconsideration of these issues.

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Traumatic Brain Injury in the War Zone

TO THE EDITOR: In Okie's Perspective article (May 19 issue)[1] on traumatic brain injury (TBI) from the war in Iraq, she alludes to mood disorders that result from such injuries. Patients with TBI have been described as the "walking wounded"[2] owing to their lingering neuropsychological problems. Lishman studied 670 cases of head injuries from the Second World War and reported that "simple measures of the amount of brain damage . . . were indeed related to the amount of psychiatric disability encountered one to five years later."[3] As many as 77 percent of patients with TBI have been given a diagnosis of depression.[4] Mood disorders may result in the restriction of social contact as well as increased loneliness and are major barriers to functional and social rehabilitation.[5]

Technological improvements and better emergency medical care have reduced the incidence of severe TBI while increasing the numbers of patients with mild or moderate TBI. Such patients are more adversely affected by their emotional problems than by their residual physical disabilities.[6] It is important to screen these patients for depression and to conduct neuropsychological testing soon after head injury in order to facilitate treatment and reentry into the community, as well as to optimize the long-term outcome.

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TO THE EDITOR: Although Okie's article described well many of the issues involved in the current war in Iraq, we would like to clarify our comments, reported in the article, regarding the classification of mild TBI. We noted that the boundary between mild and moderate TBI is one hour of loss of consciousness and that the cutoff between moderate and se-

vere TBI is one day of loss of consciousness. However, there is variation in the classification of mild TBI.

Some authors[1] use 30 minutes of loss of consciousness as the criterion, and others 20 minutes,[2] and still others[3] define "brief" loss of consciousness as lasting less than 1 hour. In practice, we more often use the duration of post-traumatic amnesia to determine the level of severity, since that information is available to us more often than are data on loss of consciousness.

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Teriparatide, Osteoporosis, Calcium, and Vitamin D

TO THE EDITOR: Dr. Licata reports in his letter to the editor (May 5 issue)[1] that the increase in serum calcium levels after treatment of osteoporosis with the parathyroid hormone derivative teriparatide correlates "inversely with 25-hydroxyvitamin D." Therefore, vitamin D supplementation to increase the level of 25-hydroxyvitamin D might be desirable. Indeed, Dr. Licata's own data show that patients with higher levels of 25-hydroxyvitamin D have a reduced risk of hypercalcemia.

Given this finding, we are very surprised that Dr. Licata advises caution in the use of vitamin D supplementation. Dr. Licata's letter focuses on the increase in levels of 1,25-dihydroxyvitamin D that accompanied the use of teriparatide, but there is much evidence that substantial vitamin D supplementation does not affect the level of 1,25-dihydroxyvitamin D.[2-4] Since 25-hydroxyvitamin D is an important determinant of serum immunoreactive parathyroid hormone in healthy adults,[5] there is still much to learn about the interrelationship between vitamin D supplementation and teriparatide.

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TO THE EDITOR: Licata describes three patients who had elevated levels of serum calcium six or more hours after receiving teriparatide (Forteo, Lilly). In a fracture prevention trial,[1] 11 percent of patients receiving 20 μg of teriparatide, as compared with 2 percent of patients treated with placebo, had at least one elevated serum calcium value in blood samples drawn four to six hours after the injection of the study drug. These elevations were not associated with adverse clinical events, and serum calcium measurements made more than 16 hours after injection of the dose were elevated in only one patient each in the teriparatide group (receiving a dose of 20 μg per day) and the placebo group. The transient rise in serum calcium after the injection of teriparatide is consistent with the known renal effects of parathyroid hormone.

The Forteo product label warns that patients with preexisting hypercalcemia should not be treated with teriparatide. The labeling for teriparatide suggests that blood samples be drawn at least 16 hours after dosing. Subsequent normalization in the serum calcium level has been observed in patients with hypercalcemia without a reduction in the dose of teriparatide or supplementation with calcium and vitamin D.[2] However, a reduction in calcium supplementation may be considered.[3]

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1. Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med 2001;344:1434-41.
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DR. LICATA REPLIES: My own observational data confirmed the lack of hypercalcemia that Dr. Krege and colleagues observed in the controlled trial of teriparatide. They are probably responding to the introductory statement that some patients developed persistent hypercalcemia — in other words, an increase in the level of serum calcium that is independent of the timing of blood sampling after drug administration. The patients in whom this problem developed would appear to have overused calcium supplements. The question is how hypercalcemia could have developed when physiologic systems are in place to limit the absorption of calcium as intake rises. The explanation may lie in the increase in 1,25-dihydroxyvitamin D that is observed in some patients. The message for practitioners is to advise patients to limit their intake of elemental calcium to that prescribed.

The observations of Drs. Vieth and Cole are points well taken. Today there is great concern about vitamin D deficiency. Experts are intimating that higher doses of the vitamin should be considered in our guidelines. The suggestion that patients receiving teriparatide should limit their supplementation of vitamin D seems counterintuitive, as they suggest. Normal physiologic mechanisms limit the increase in levels of 1,25-dihydroxyvitamin D despite substantial supplementation with vitamin D. However, this normal regulation may not be the case with teriparatide. In some patients, levels of 1,25-dihydroxyvitamin D increase despite regulatory signals that should have prevented it (i.e., increased levels of serum calcium and decreased levels of intact parathyroid hormone).

This finding may reflect a lack of normal regulation reminiscent of sarcoidosis, in which normal physiologic control of 1,25-dihydroxyvitamin D is absent and vitamin D intake has a direct effect on the production of 1,25-dihydroxyvitamin D and on serum calcium levels.[1,2] Obviously, teriparatide (a drug) and sarcoidosis (a disease) are quite different. But the similarities as noted should give us pause. We do not yet fully understand the interrelationship of this type of drug and vitamin D. Present clinical experience arises from the use of anticatabolic drugs, which are distinctly different from this type of drug. This concern could be a false alarm, but until we have more data, it seems prudent for clinicians to be more vigilant and to elicit information about which nonprescribed supplements and vitamins patients are taking.

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BOOK REVIEWS

PEDIATRIC RETINA: MEDICAL AND SURGICAL APPROACHES

Edited by Mary Elizabeth Hartnett, Michael Trese, Antonio Capone, Jr., Bronya J.B. Keats, and Scott M. Steidl. 559 pp., illustrated. Philadelphia, Lippincott Williams & Wilkins, 2005. $249. ISBN 0-7817-4782-1.

"Invisible by design, vitreous was long unseen as an important participant in the physiology and pathology of the eye." Thus begins an early chapter in this exhaustive and often eloquent textbook on pediatric retinal development, disease, and surgery. Devoting an entire chapter to an invisible structure, and making it imaginable and vital, is just one of the accomplishments of this essential book.

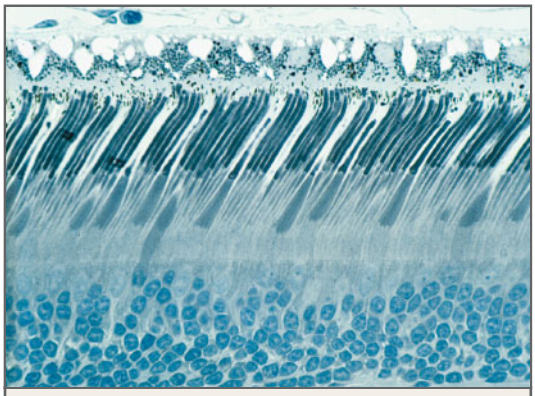
Why ophthalmologists are superspecialized becomes apparent in a book such as *Pediatric Retina*. The eye is a world, and each structure in it is distinct. The transparent, avascular cornea and lens focus images onto the tissue-paper-thin yet multilayered retina through the vitreous, a clear gel that gradually liquefies with age. Then there are the extraocular muscles, eyelids, orbits, and finally, the optic nerve, which connects the eye to the visual cortex in the brain. Each structure has its own genetics, metabolism, and surgical idiosyncrasies, which can be fully understood only by single-minded study and practice.

Is a textbook on the pediatric retina necessary? The answer is yes. To adapt a mantra from general pediatrics, infant eyes are not simply small adult eyes. This book conveys that idea beautifully, from the chapters on embryology, with the accompanying clinical correlations with disordered development, to the final section on visual rehabilitation by the internationally respected pediatric specialist in low vision Lea Hyvärinen. Although in children two years of age the eye is 95 percent of adult size, important differences in the vitreous make some adult surgical techniques difficult and others impossible in such children. Many retinal surgeons avoid children's eyes; others dive into such work. This book is by and for the latter group and for their colleagues in related fields.

Far more than a surgical textbook, this book includes chapters by noted experts on such topics as genetic counseling, anesthesia in children, tumors, uveitis, and posterior pole imaging. There are important chapters on the clinical assessment and management of retinal diseases requiring surgery in infants and children. Many of these chapters are coauthored by two of the editors, Michael Trese and Antonio Capone, Jr., both of whom are pioneers in pediatric retinal surgery and have singular insights into special techniques for young eyes. The descriptions and images of surgical approaches will be invaluable to anyone who performs pediatric retinal surgery. Specialized instruments are pictured, with vendors listed, and excellent drawings depict the ocular entry sites for and uses of these instruments.

Retinopathy of prematurity is a leading cause of blindness among children in the United States. An authoritative chapter discusses the major clinical trials, which are summarized in a table, and how each has advanced our understanding of the disease. Another chapter describes how retinopathy of prematurity progresses to blind an eye and the complex treatments that can be tried to halt or reverse blindness. This chapter should be required reading for anyone taking on the mission of fighting this devastating disease.

Despite advances, many retinal disorders are still



Section through the Retina Showing Rods and Cones in the Photoreceptor Layer of an Adult.

Chris Guerin/Wellcome Photo Library.

blinding. Hope — a necessity for physicians, parents, and patients — features prominently in the chapters on gene therapy, retinal transplantation, and visual prostheses (also called "retinal microchips"). Subretinal, epiretinal, optic-nerve, and cortical implants can electrically stimulate the remaining components of damaged visual pathways to create artificial vision. Clinical trials are under way, and "vision" has been demonstrated. Gene therapy to replace defective genes or gene products has already shown some success in dogs with a form of congenital retinitis pigmentosa. An innovative table in the book lists pediatric retinal disorders that might be amenable to gene therapy, as well as potential strategies.

The book ends with a bonus: the Appendixes. The first one contains a list of genes that cause retinal diseases, and this is followed by eight others dedicated to several retinal disorders that are illustrated in beautiful color photographs. Ophthalmology is a supremely visual field, in that it requires the physician's direct sight, rather than hearing or touch, for diagnosis and treatment, including surgery. Arguably, retina is its most visual subspecialty. The editors conclude the book with a worthy tribute to their field, which will be of great value to medical students, residents, and practicing ophthalmologists.

Among retinal specialists and pediatric ophthalmologists, this book is likely to become a classic. It will be most appreciated, however, by those few daring souls who combine these two fields to pursue this highly specialized, risky, and rewarding subsubspecialty, pediatric retina.

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WALSH AND HOYT'S CLINICAL NEURO-OPHTHALMOLOGY

Sixth edition. Edited by Neil R. Miller, Nancy J. Newman, Valérie Biousse, and John B. Kerrison. 3573 pp., plus index, in three volumes, illustrated. Philadelphia, Lippincott Williams & Wilkins, 2005. $699. ISBN 0-7817-4814-3.

Nearly every neuro-ophthalmolgist owns at least one edition of *Walsh and Hoyt's Clinical Neuro-Ophthalmology*. Throughout the years, appropriate descriptors have included encyclopedic, exhaustive, authoritative, comprehensive, and up to date. The editors and more than 60 contributing authors continue this tradition with the sixth edition of this book.

Written and edited by some of the leading authorities in neuro-ophthalmology, each section provides a historical perspective, an extensive exposition of clinical features including personal observations about the topic under discussion, diagnostic approaches, and suggestions for treatment. Volume I covers disorders of the visual system, eye movements, pupils, eyelids, and headache. The scope of this volume extends beyond topics related only to the eye. Volume II is devoted to tumors of the nervous system, the phacomatoses (multiple hamartomas of the central and peripheral nervous system, eye, skin, and viscera), and vascular disorders. Volume III encompasses degenerative, metabolic, inflammatory, and demyelinating diseases. The section on infections of neuro-ophthalmic significance is outstanding. It alone could serve as a separate book.

The editors have reduced the size of the book from the five volumes of the fifth edition to a more manageable three, trimming approximately 2000 pages without a noticeable decline in quality. They eliminated 11 chapters by incorporating their content into related chapters. The number of references at the end of each chapter is staggering. The list for most chapters consists of 400 to 700 references, but the lists for the chapters on viruses and bacteria have more than 2000 each. Although computerized search engines easily identify articles from 1950 to the present, *Walsh and Hoyt's Clinical Neuro-Ophthalmology* includes references to older, pertinent literature, and the value cannot be overstated.

No book or set of books is perfect. Unfortunately, this book has only black-and-white figures, but they include an impressive collection illustrating even the rarest of disorders. For a book consisting of such a prodigious number of topics, I feel that a more extensive, cross-referenced index would have been more helpful. For instance, the index lists oculopharyngeal muscular dystrophy under "muscular dystrophies." If readers choose to search under "oculopharyngeal muscular dystrophy," they will not find a listing or cross-reference. A minor irritation is that the page numbers are not listed on the outside of each volume. When I tried to look at page

2430, I initially pulled Volume III, which begins at page 2469.

At 3573 pages, *Walsh and Hoyt's Clinical Neuro-Ophthalmology* represents an outstanding book and an essential reference for anyone interested in the field. It covers every aspect of neuro-ophthalmology that I chose to look up. Neurologists, neurosurgeons, and ophthalmologists will definitely benefit from this book. I hope that one day the publisher will issue an electronic version on CD-ROM to facilitate searching this vast resource of neuro-ophthalmology.

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PERINATAL NUTRITION: OPTIMIZING INFANT HEALTH AND DEVELOPMENT

(Nutrition and Disease Prevention.) Edited by Jatinder Bhatia. 379 pp. New York, Marcel Dekker, 2005. $179.95. ISBN 0-8247-5474-3.

Good nutrition is essential for increasing survival rates among infants born prematurely in resource-rich countries and among those born in poorer circumstances — babies who often have low birth weight despite having had a full-term delivery. Such infants are at long-term risk for growth failure and substantial morbidity and mortality due to malnutrition. This book, a compilation of scientific and dietary advice regarding perinatal nutrition and nutrition in pregnant and lactating mothers, is timely, and its mixture of practical, "how to" chapters and those on theoretical topics will appeal to a wide range of readers.

Currently, dietary recommendations in the United States are in a state of flux. The well-known recommended dietary allowances (RDAs), most recently revised in 1989, have been replaced during the past eight years by a series of dietary-guideline books that contain unfamiliar new terms such as "estimated average requirement" and "upper limit." Food labels continue to use the daily values, which are actually based on the 1968 RDA values and are frequently not easily adapted to the needs of small children or their mothers. There are additional dietary recommendations for infants in the Infant Formula Act and many authoritative panel statements by the World Health Organization (WHO). It is therefore necessary to be cautious about applying any set of guidelines, including those in this book, to such a rapidly changing target.

Unfortunately, this book mixes together old and new guidelines and their conflicting advice. This is particularly problematic for the maternal recommendations in chapter 3, which follow 1989 RDA values in recommending that daily calcium intake increase substantially during pregnancy. Chapter 2 accurately notes that an increase in calcium intake has not been recommended in the United States since 1997, when guidelines noted that such a change was not supported by scientific evidence.

Other controversies do not clearly reflect consensus views. For example, a long chapter on weaning contains multiple references to the view of a single scientist who believes that breast-fed babies require supplementation of iron from birth. Although an opposing view is indicated, it is not clear from the text that recent position statements by the WHO and the American Academy of Pediatrics recommend against the introduction of solid foods or iron supplements to the diet before six months of age for healthy, full-term, breast-fed infants.

The book closes with a remarkable chapter regarding the ethics of withholding nutrition from terminally ill neonatal patients. This clear discussion of a timely topic is well worth careful reading and consideration. The view that death by withdrawal of nutrition from appropriate palliative care in terminal cases is "comfortable" is consistent with my experience and is a most welcome contribution to the discussion of this topic. Neonatal caregivers at the forefront of such difficult decisions are in need of this kind of discussion before they themselves become headlines.

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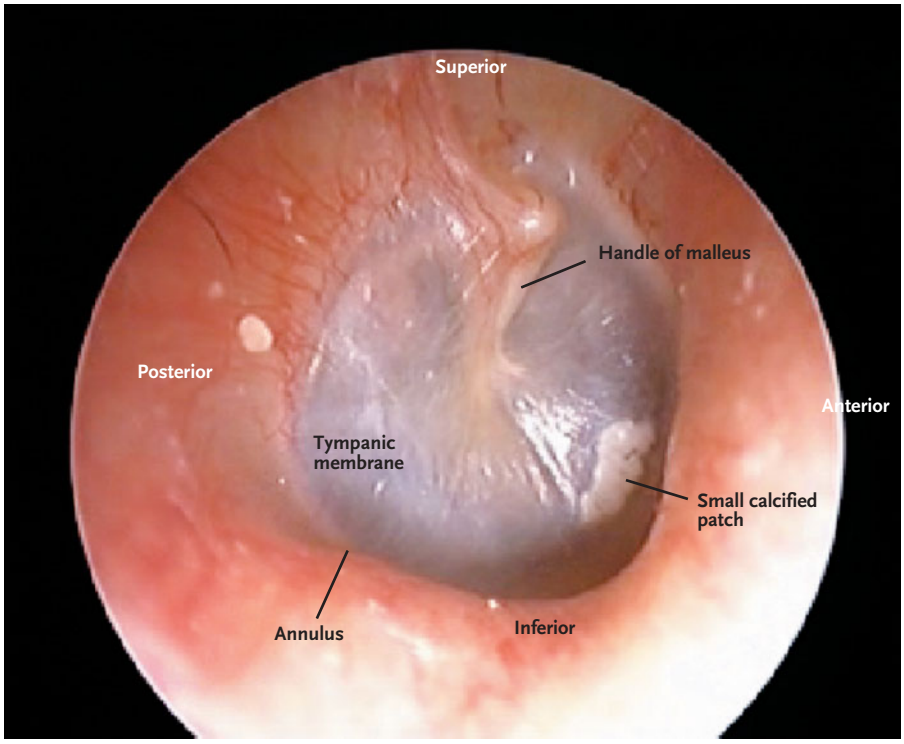
IMAGES IN CLINICAL MEDICINE

Patulous Eustachian Tube



A healthy 26-year-old man reported a three-month history of aural fullness and a flapping noise in his right ear. Otoscopy revealed inward-and-outward movements of his right tympanic membrane in time with his nasal respiration (Video Clip 1). Both the symptoms and the motion in his eardrum were greatly reduced when he lay down. We diagnosed a patulous eustachian tube, signifying abnormal patency of the tube. This anomaly permits the movement of air into and out of the middle ear by means of the eustachian tube during nasal breathing. The tympanic membrane moved outward when the patient exhaled, owing to the transmission of positive nasopharyngeal air pressure (relative to the atmospheric pressure) to the middle ear. When the patient inhaled, the tympanic membrane moved inward because of the opposite mechanism. Adopting a recumbent position relieved the symptoms because of increased venous stasis and passive compression of the eustachian tube.

A patulous eustachian tube is associated with pregnancy, rapid weight loss, mucosal atrophy (e.g., that due to atrophic rhinitis or occurring after radiotherapy), or muscular dysfunction. In many instances, however, a satisfactory explanation cannot be found, as was the case with this patient. The patient was treated with the insertion of a grommet into the right tympanic membrane, which led to the resolution of his symptoms.

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