

# A Mariner with Crippling Arthritis and Bleeding Eyes

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**ABSTRACT:** A 41-year-old mariner developed acute arthritis affecting his legs more than his arms or hands during a violent storm on his return from the first of four voyages of discovery. He experienced repeated attacks of the arthritis over the ensuing 14 years, which on at

least two occasions were accompanied by painful eyes "much affected with bleeding." He died shortly before his 55<sup>th</sup> birthday "quite paralyzed and bedridden." Who was he, and what was the likely etiology of his disorder? [*Am J Med Sci* 2006;332(3):123-130.]

## Presentation of Case<sup>1,2</sup>

The patient's illness began abruptly at age 41 with an attack of the gout during a violent storm on his return from the first of four voyages of discovery. Its nature is uncertain but seems to have consisted of an intermittent, though relentlessly progressive, polyarticular arthritis affecting the legs more than the arms or hands. Acute attacks most often coincided with exposure to cold and dampness while the patient was at sea. Malnutrition and chronic insomnia also may have contributed to the disorder, in that some of the most severe attacks occurred during times of poor nutrition and sleep deprivation.

Although it has long been maintained that the patient was a Genoese Christian by birth, some scholars now believe he was the son of Catalans, and that his mother might have been a member of a prominent *converso* (converted Jew) family. We know almost nothing of his family's medical history. If he was the man from Genoa he is generally considered to be, he had a younger sister and three younger brothers (one of whom died at an early age of unknown cause). No other family member is known to have had the gout.

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However, post-mortem examination of remains presumed to be those of the patient's brother (possibly of the patient himself) show fusion of the 4th and 5th lumbar vertebrae and incomplete spina bifida. Identical abnormalities are present in the remains of one of the patient's sons.

The patient was a mariner and an explorer. His writings demonstrate fluency in Latin as well as more than a passing knowledge of the works of Aristotle, Ptolemy, Marinus of Tyre, Strabo, Pliny, and Marco Polo. Therefore, he seems to have been well educated. However, neither the source nor the extent of his formal education (if any) is known. He married at age 28. His wife (a Portuguese noblewoman) died 6 years later of unknown cause after having produced a son. The patient then took a mistress, by whom he had a second son. Whether he had other sexual relationships is not known. However, sexual promiscuity was common among the men who served under him, many of whom contracted syphilis.

Prior to his 41st year, the patient's only recorded medical problem was a wound of unknown location and severity received in a sea battle at age 25. At that time he also was crippled temporarily after swimming two leagues from his wrecked ship to the nearby shore.

As a young man, the patient was "tall, well formed, muscular, and of an elevated and dignified demeanor . . . his complexion fair and freckled, and inclined to ruddy.... his eyes blue.... his hair... a light color [which] care and trouble.... soon turned it grey.... [and then] quite white." He was sober and moderate in eating and drinking.

The patient seems never to have recovered fully from his initial attack of the gout. In December of the year following his first attack, he and many of his men came down with an illness believed to have

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been influenza. Whereas most of the others recovered quickly, the patient had unspecified complications which took nearly 4 months to resolve. At age 43, while sailing in the vicinity of Puerto Rico, he developed "fever and somnolence, which suddenly deprived him of his sight, his other senses, and his memory." Another attack of gout ensued, so severe that he was incapacitated for more than 5 months.

At age 47, the patient suddenly "was seized by grievous pains of gout in the leg, and four days after by a terrible fever, but despite his illness, he remained sound of mind." Two months later, "his eyes [became] so much affected with bleeding and [were] so painful" he had difficulty seeing. His letters at that time were rambling and incoherent. A prolonged period of enforced rest temporarily restored his health. However, by age 51, he was "already an aged man according to the notions of his day." In fact, during his fourth and final voyage of discovery, he was so sick and so frequently lay at death's door, he had to issue orders from a doghouse he had constructed on the poop deck of his flag ship. In the midst of his deteriorating health, his old wound opened up. During an exhausting and humiliating year marooned on the island of Jamaica, he was shaken by a malaria fever, which rendered him delirious, and arthritis so severe he could not stand.

After Jamaica, the patient's condition declined rapidly, and although a prolonged period of rest brought modest relief, by his 54th year, his arthritis was so severe, most of the time he was confined to bed. In cold weather, his agony was unbearable. Toward the end, his hands were so painful, he could no longer write. Finally, on May 20, 1506, shortly before his 55th birthday,\* "already quite paralyzed, bedridden with the gout," the patient died.

### Differential Diagnosis

*Dr. Frank C. Arnett:* Our patient was a 15th Century Genoese mariner and explorer, with "more than a passing knowledge of the works of Marco Polo," who undertook 4 voyages to the New World, including Puerto Rico and Jamaica. Given that profile, his identity is not difficult to discern. Most assuredly, the patient was Christopher Columbus.

What is not known by most people is that beginning at age 41, Columbus was plagued by relapsing arthritis which left him crippled when he died in 1506 at nearly 55 years of age. He was said to have had gout; however, at that time, most forms of arthritis, including those to follow in my differential diagnosis, were called gout.

*\*Note: The date of the patient's birth is uncertain. The ages given in this protocol reflect the most widely accepted chronology of his life. However, some authorities believe that the patient actually lived to be 60 to 70 years of age and that 7 or 8 years should be added to the ages listed in this Case Summary.*

From the protocol, how can our patient's disease best be characterized? It clearly was a relapsing and predominantly lower extremity arthritis that tended to disable the patient for months on end and eventually crippled him. It seems to have recurred most often while the patient was at sea, was accompanied by fever and often delirium, and appeared to follow, at least in one instance, a shipboard epidemic of a flu-like illness. Whether the flu-like illness was respiratory or gastrointestinal in nature is not clear. Perhaps most discriminating among the clinical features recorded is the recurrent eye disorder described as bleeding, painful, and, at times, causing blindness. These episodes appear to have paralleled the attacks of arthritis and, I believe, provide one of the most helpful clues to the diagnosis.

Several forms of arthritis should be considered in the differential diagnosis based on their typical patterns and courses, other accompanying clinical manifestations, and the potential genetic and environmental predilections of this patient. First, could Columbus really have been afflicted with gout as stated in his case summary? Certainly, this is not an unreasonable diagnosis in a 41-year-old man with an acute and incapacitating arthritis affecting one or more joints of the lower extremities. In its early stages, gouty arthritis is an episodic illness in which attacks may be accompanied by fever. Moreover, without the treatments available today, the natural history of gout is to become polyarticular, with later involvement of the upper limbs and hands, and culminating in a chronic, crippling disorder (tophaceous gout).<sup>3</sup> Columbus, however, was not the stereotypical, portly man inclined toward purine-rich foods and alcohol intemperance. Instead, he is said to have been "sober and moderate in eating and drinking." A stronger argument against his having gout concerns the duration of his attacks. At least early in the course of gout, flares of arthritis typically last 7 to 10 days and then resolve completely. In this case, "the patient seems never to have recovered fully from his initial attack of the gout." He experienced many months of disabling arthritis on several occasions before becoming bedridden by the disease. Finally, the ocular symptoms, if related to the basic illness, cannot be explained by gout.

A few other episodic or relapsing forms of arthritis are worth considering, however briefly. Rheumatic fever was likely a scourge of the 15th century, especially on board vessels in which overcrowding favored the spread of streptococcal infections.<sup>4</sup> What is more, according to past medical lore, the typical host for rheumatic fever was fair-skinned and freckled—precisely the complexion attributed to Columbus above. Rheumatic fever, however, while prone to recur, causes a migratory arthritis, usually of large joints, which is nondeforming and of only a few weeks' duration. Moreover, it does not attack the eyes.

Could Columbus have had rheumatoid arthritis, a potentially crippling inflammatory arthritis that to-

day affects approximately 1% of the world's population? "Bleeding of the eyes" might describe the scleritis occasionally complicating rheumatoid arthritis. Without entering the debate about whether rheumatoid arthritis even existed before the 19th century,<sup>5</sup> it is not likely Columbus' diagnosis. For one thing, the pain of rheumatoid arthritis is typically not as excruciating as his seems to have been; for another, early involvement of the hands is nearly universal; the course is generally unremitting; and fever is unusual.<sup>6</sup>

Because Columbus came from the Mediterranean, several diseases endemic to that region should at least be mentioned. Familial Mediterranean fever, while episodic, is characterized by monthly fevers, bouts of serositis (peritonitis, pleurisy, pericarditis), and sometimes nondeforming arthritis.<sup>7</sup> This was not Columbus' clinical picture. Similarly, Behçet disease may be dominated by a nondeforming arthritis and severe uveitis, but in the absence of painful oral or genital ulcers, this diagnosis is not viable.<sup>8</sup>

Scurvy, an occupational hazard of early mariners, could explain excruciating joint or bone pain caused by bleeding into musculoskeletal structures, "bleeding eyes" (conjunctival hemorrhage), and even opening of an old wound. Columbus' voyages, however, were relatively brief, with none lasting the 3 months typically required for scurvy to develop.<sup>9</sup>

There is another disorder, however, namely reactive arthritis, that could explain all of the clinical features of Columbus' illness. For many years, it was called "Reiter syndrome" (or disease) and, as classically described, includes the triad of urethritis, conjunctivitis, and arthritis<sup>10,11</sup>; uveitis also occurs. The syndrome has been proposed previously as the cause of Columbus' illness.<sup>12</sup>

Reactive arthritis was long believed to be a sterile arthritis and enthesitis (inflammation of tendon insertions/attachments) initiated by an infection distant from the joint.<sup>13-15</sup> Several large outbreaks of reactive arthritis following epidemics of gastroenteritis have implicated a number of enteric pathogens as etiologic agents<sup>14,16,18</sup> (Table 1). Epidemiologic investigations have also incriminated a variety of sexually transmitted pathogens, such as *Chlamydia trachomatis*.<sup>19,20</sup> In fact, before the advent of the HIV epidemic in the early 1980s, reactive arthritis was the most common cause of arthritis in young men in the US military<sup>17,21</sup> and, perhaps, in the general population as well.<sup>22</sup> Now it is much less common, presumably because of safer sexual behavior<sup>23</sup> and better protection of the food supply in developed countries.

Recently, we have discovered that reactive arthritis, strictly speaking, is not sterile. *Chlamydia trachomatis* has been identified in synovial tissues of patients with reactive arthritis and appears to be able to persist in a viable state for years.<sup>13-20</sup> Bacterial fragments of enteric pathogens have also been

**Table 1.** Microbes Causing Reactive Arthritis

Enteric Pathogens
<i>Shigella flexneri</i>
Salmonella (many species)
<i>Yersinia enterocolitica</i>
<i>Yersinia pseudotuberculosis</i>
<i>Campylobacter jejuni</i> Sexually
Acquired Pathogens
<i>Chlamydia trachomatis</i> ?
<i>Ureaplasma urealyticum</i> ?
Respiratory tract infections ?
<i>Chlamydia pneumoniae</i>

detected in the joints of such patients many years after the initial infection.<sup>15,24,25</sup>

Genetic characteristics determine both susceptibility to and the severity of reactive arthritis.<sup>26</sup> HLA-B27, a major histocompatibility complex (MHC) class I molecule involved in cytotoxic T lymphocyte responses, is present in approximately 75% of patients with reactive arthritis. HLA-B27, in fact, is a major genetic marker for a whole family of diseases referred to as spondylo-arthritis<sup>13,26</sup> (Table 2). Therefore, if Columbus had reactive arthritis, which seems likely, based on the nature of his complaints, in all probability he also had the HLA-B27 genotype.

The frequency of HLA-B27 in the general population varies widely. In European Caucasians, the highest frequencies are found in the most northern countries<sup>26-31</sup> (Figure 1). That Columbus was tall, fair-skinned, and blue-eyed suggests that he had a northern European ancestry and thus a relatively high likelihood of having inherited HLA-B27. Approximately 20% of HLA-B27-positive persons infected with one of the pathogens listed in Table 1 develop reactive arthritis within 2 to 4 weeks of the infection.<sup>15</sup>

The precise role of HLA-B27 in the pathogenesis of reactive arthritis is not yet clear, despite discovery of the genetic association over 30 years ago.<sup>32,33</sup> We do know that the HLA-B27 molecule is directly involved because when human HLA-B27, but not other HLA genes, is introduced into certain strains of transgenic rats, the animals spontaneously develop nearly all the clinical features of reactive arthritis.<sup>34</sup> When raised in a germ-free environment, such animals remain disease free.<sup>35</sup>

**Table 2.** The Spondyloarthritis Family of Diseases Associated with HLA-B27

Disease	% Positive for HLA-B27
Ankylosing spondylitis	90
Reactive arthritis	75
Psoriatic spondylitis	50
Enteropathic spondylitis associated with Crohn disease and ulcerative colitis	50
Acute anterior uveitis	60



Figure 1. Frequencies of HLA-B27 in selected countries in Western Europe.

There are a number of ways in which HLA-B27 might predispose to reactive arthritis<sup>36-39</sup>: 1) HLA class I molecules, such as HLA-B27, are composed of a heavy chain (the HLA gene product) and a light chain (B<sub>2</sub>-microglobulin) complexed as "heterodimers" on the surfaces of all nucleated cells. The polymorphic regions of these molecules surround an antigen binding groove or cleft having a specific "motif with which it binds polypeptides composed of specific amino acids. Like other HLA molecules, HLA-B27 has its own unique antigen binding motif that theoretically binds and presents to T cells "arthritogenic" peptides derived from particular bacteria, perhaps even from the host itself. In this respect, molecular mimicry between self and bacterial antigens might induce an autoimmune reaction responsible for reactive arthritis; 2) HLA-B27 also is unique among HLA class I molecules in that two of its alpha chains can associate to form an autoantigenic "homodimer" capable of inducing an aberrant immune response; and 3) in vitro studies have shown that HLA-B27-positive monocytes have difficulty killing intracellular *Salmonella* and might therefore predispose the host to reactive arthritis by allowing such pathogens to persist.

The fact that only 20% of HLA-B27-positive persons who encounter one of the causative bacteria develops the disease suggests that other genes are involved in susceptibility to reactive arthritis. Currently, large genome-wide scans are underway to identify such genes, and it appears that, while HLA-B27 exerts the

most powerful effect, additional loci within the major histocompatibility complex (MHC), as well as genes on other chromosomes, are also involved in the pathogenesis of reactive arthritis.<sup>26</sup>

The course of reactive arthritis is entirely consistent with Columbus' illness. Although most patients with reactive arthritis recover completely within 6 to 12 months, some have a relapsing or progressive course.<sup>22-40</sup> HLA-B27 is found in nearly all those who have a chronic course, as well as those who develop uveitis, the condition I believe was responsible for Columbus' eye problems.<sup>33-40-41</sup> Thus, HLA-B27 determines the severity of reactive arthritis, just as it determines susceptibility to the disorder. It is likely that repeated exposures to one or more of the causative bacteria worsens prognosis, and Columbus may have had multiple encounters with enteric or sexually acquired infections during his voyages to the New World.

The fusion of the fourth and fifth lumbar vertebrae of Columbus' brother and son is also relevant. Although these might simply be congenital anomalies, spinal fusion occurs in ankylosing spondylitis, another HLA-B27-associated disease, which was not to be described for another 200 years.<sup>42</sup> Approximately 10% to 12% of patients with reactive arthritis develop spondylitis.<sup>13,40</sup>

Did Columbus' reactive arthritis kill him? Certainly, it caused him to be bedridden for prolonged periods and therefore would have predisposed him

to both pneumonia and pulmonary emboli. Chronic inflammatory disorders are also associated with atherosclerosis and premature cardiovascular death.<sup>43</sup> If Columbus died as a direct result of his reactive arthritis, then aortic valvular regurgitation and/or heart block (spondylitic heart disease),<sup>44</sup> or secondary amyloidosis might have killed him.<sup>45</sup>

Had Columbus lived today, the severity of his arthritis would almost surely have dictated treatment with one of the new tumor necrosis factor (TNF) alpha antagonists.<sup>38</sup> In all likelihood, his symptoms would have been dramatically reversed and his crippling and premature death prevented. Conceivably, a still vigorous and relatively young Columbus could have made more discoveries or further influenced the development of the New World. Perhaps today we might even live in North Columbia rather than North America had modern medicine existed during the Age of Discovery.

#### Dr. Frank C. Arnett's Diagnosis

HLA-B27-associated reactive arthritis precipitated by recurrent bacterial gastroenteritis or a sexually transmitted infection.

#### Historical Discussion

*Dr. Charles Merrill and Sr. Francesc Albardaner:* One of the sights travelers to the Italian city of Genoa are directed to see is a handsome stone dwelling called "La Casa di Colombo" (the House of Columbus) purported to be the one in which the discoverer of America grew up. If you look up "Columbus, Christopher" in encyclopedias and history texts you will find they all say that, whether in that very house or not, he was born in or around Genoa in 1451 of Genoese parents who belonged to what we would call the lower middle-class. According to this standard account,<sup>2</sup> he began life as a sailor on voyages from that port at an early age. In 1476 he settled in Portugal. There he became obsessed with the idea of sailing west to find Asia (not, by the way, to prove that the world is round). He moved to the Kingdom of Castile in 1485 to seek support for his plan. He got it, and made four voyages across the Atlantic, and though he never arrived in Asia, he gained immortal fame for finding what he did. He never went back to Italy, but he loved his native city and provided in his will that a family member should live and be supported financially in Genoa. He died in Spain in 1506, and is buried there, or in Santo Domingo, or in Havana.

We know all of this because, according to this standard account, Columbus himself said in his will and in some letters, that he was born in Genoa; because early historians called him Genoese, or at least Ligurian; because he was not identified with any other nationality; and because we have records of a *Cristoforo Colombo* who was born in Genoa in 1451 and later went to Portugal.

So, why are there those who have come to doubt Columbus' origin as described in this standard account? First of all, Columbus never claimed, in any of the 536 pages of his *Letters and Documents* published in the standard edition, to have been from Genoa, or from anywhere else.<sup>46</sup> Although Cristoforo Colombo's father and other relatives were living in Genoa after 1492, the Admiral, Cristobal Colon, who the standard account maintains was one and the same with the man Cristoforo Colombo from Genoa, never wrote to these relatives or referred to them in any way.

A number of official documents still exist from Columbus' years in the Kingdom of Castile, of the sort in which one might expect his origin to be named. The earliest ones are notes of payment issued by the treasurer Francisco Gonzalez in 1487 and 1488. In the first, he is called "Cristobal de Colomo, foreigner." In the other three "Xrobal Co-lomo," with no qualifying adjective after his name-not even "foreigner," much less "Genoese."<sup>47</sup>

In fact, in no official document found in the Castilian or Aragonese state archives is Columbus' nationality stated. And this lapse is by no means consistent with standard procedure of that time, according to which foreigners in the Kingdom of Castile were always identified in documents drawn up in the royal chancery by an adjective of nationality: "Fernando Magallanes, Portuguese," for example, or "Americo Vespucci, Florentine."<sup>48</sup>

What about other contemporaries? It is surely significant that the ambassadors from the state of Genoa to the court of Ferdinand and Isabella, who were at the court in Barcelona when Columbus returned from his first voyage in 1493, said not a word about the brilliantly successful explorer's being one of their countrymen in letters they wrote to Genoa. Furthermore, when the Signoria of Genoa wrote to the King of Aragon expressing their satisfaction with the treaty the ambassadors had negotiated, they mentioned the voyage of discovery, but did not mention Columbus. Is it conceivable that they would have failed to do so if they had thought he was from Genoa?<sup>49</sup>

But what does any of this matter? Some early chroniclers may not have identified him as Italian, and some of the ones who did may have done so less straightforwardly than we might wish, but so what? We know that Columbus was Italian because we have archival documents<sup>50</sup> which attest to a Cristoforo Colombo, born in 1451 in Genoa, grandson of Giovanni Colombo, nephew of Battistina and Antonio, son of Susanna and Dominico Colombo, a Genoese citizen, cheese-wright and wool-merchant. He was in Portugal in 1479, and does not appear in Genoese documents after that time because he had moved to the Kingdom of Castile and was busy discovering America.

Six of the documents, dated between 1470 and 1473, mention a Cristoforo Colombo, who is called a

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wool weaver or merchant, like his father. None of them gives any indication that he ever went to sea. The only Genoese document, in fact, which connects Colombo with sailing is a copy of a deposition made at a hearing in 1479 (pp 30-31 in ref. 50), in which Cristoforo Colombo, citizen of Genoa, declares that he is leaving for Lisbon the next day—presumably by boat—and that he had been in Lisbon the year before, where he had been a party to a failed business deal involving a voyage—certainly by boat—to Madeira to purchase sugar. But from none of the Genoese documents, including this one, can it be concluded that Colombo was a mariner, who actually engaged in sailing or navigating ships. When modern biographers talk about voyages in the Mediterranean and the Atlantic made by Christopher Columbus of Genoa before 1492, they are assuming that the Genoese Colombo is the same man as Cristobal Colon, who claimed to have been a sailor since he was 14 years old.

But rather than accept that assumption, let us compare the man who arrived in the Kingdom of Castile in 1485 and came to be known as the Admiral Cristobal Colon with the cheesemonger, Cristoforo Colombo of Genoa. When we do, the first thing we notice is that the Admiral never called himself Cristoforo Colombo, nor did anyone who knew him. His surname was always given as Colom, or Colomo, or Colon. The first time he was called Colombo was in an Italian translation of a Latin text written in 1493 in which he was called Colom and Columbus, which, like Colombo, mean "dove."

Secondly, the two men were not the same age. Colombo was born in 1451, and would have been not quite fifty-five when he died in 1506. But the Admiral was older. He was said to have been "of a ripe old age"<sup>51</sup> in 1506, and no one in the 15th or 16th century considered almost fifty-five to be a ripe old age.

Thirdly, they were of different social classes. Colombo was a wine and cheese merchant. Columbus-Colon was called noble and *don*, had a coat-of-arms, and married a Portuguese noblewoman, all before his return from the successful voyage of 1492.

In addition, they differed with regard to their education. We know that Columbus-Colon was an educated man who had learned to write at an early age and had read widely in Latin, Spanish, Italian, and Catalan in the fields of cosmography, geography, natural science, and history. He was not a scholar but did acquire a considerable degree of general and specialized knowledge, and he did so before arriving in Andalusia. This much education simply does not fit the Genoese Cristoforo Colombo.

Also, Colon-Columbus was an experienced mariner long before his first voyage to the New World. He had commanded a ship as early as 1472, and all of his contemporaries, and most modern historians, agree that he was one of the finest sailors and navigators of his day. More than likely, he sailed with an expedition

sponsored by the kings of Portugal and Denmark to Greenland and Iceland—and perhaps beyond—in 1477.<sup>52</sup> Because he did no sailing between 1485 and 1492, he had to have gained considerable experience early in life. But from all we can tell from the available documents, Cristoforo Colombo, who was still called a wool-worker in 1473 and who never identified himself nor was identified by anyone else as a sailor, had no early experience commanding crews and sailing ships.

Also, there are no references to Columbus ever having spoken or written Genoese or Italian. Everything he wrote which survives, including letters to his brothers and to Genoese and other Italians, is in Latin or Spanish. Those who identify Colombo with Columbus see no difficulty with this. And yet, at the very least, it seems odd that a Genoese who learned to write at an early age, never wrote notes to himself or letters to his brother in his native language, nor did Italians do so when they wrote to him.

Well, if Columbus was not Genoese, what was he, and why might he have been reluctant to reveal his true nationality? The answer, we believe, lies in the geopolitics of the world he inhabited.

When Columbus was born in the mid 1400's<sup>1</sup>, Europe was a complex puzzle of Christian kingdoms and republics, some of which no longer exist. One of the richest and most powerful states of that time was one few today have even heard of, namely the Catalan Empire, a confederation of kingdoms and territories that included Catalonia, Aragon, Valencia, the Balearic Islands, Sardinia, Sicily and the territories of the Kingdom of Naples. Because these vast territories have since been incorporated into Spain, France, Italy, and Andorra, there is no longer an independent country of Catalonia. But in the 15th century, Catalonia was a distinct geopolitical entity, inhabited by a people who spoke the Catalan language. Columbus, we believe, was one of them.<sup>53</sup>

For one thing, Columbus' original and, hence, true family name, Colom, the one used in the famous letter to Lluís de Santangel (now residing in the New York Public Library) announcing the discovery of the New World, is a Catalan surname. Moreover, whereas all of Columbus' surviving manuscripts are written in Castilian, that is in Spanish (even letters he wrote to Italians), his Castilian is imperfect, and therefore, not likely his mother tongue. If not Castilian, what was his mother tongue? Professor Lluís d'Yzaguirre,<sup>54</sup> member of the Pompeu Fabra University of Barcelona, believes it was Catalan. He bases his conclusion on lexicometric examination of all of Columbus' known manuscripts, which identified an Eastern Catalan linguistic variant (peculiar to the area between Roussillon and the area south of Bar-

<sup>1</sup> Note: Opinions about the year of the birth of Columbus range from 1436 to 1451, according to the various historians who have studied the issue. We consider 1442 to be the most probable date.

celona) hidden behind a veil of imperfect Castilian. Similarly, forensic analysis of Columbus' handwritten texts by Father Gabriel Roura, director of the Capitular Archive of the Cathedral of Girona and former professor of paleography of the Autonomous University of Barcelona and the University of Girona, shows evidence of a 15th century Catalan style of calligraphy characteristic of a man educated in a Cathedral school.<sup>55</sup>

If the Catalan theory is correct, Columbus' reason for concealing his true identity most likely concerned his activities during the Catalan civil war of 1462-1472, in which he is believed to have participated in an attack on four ships belonging to Ferdinand's cousin, King Ferrante of Naples, while a captain in the navy of Rene d'Anjou. Several historians agree that the attack took place in 1472 or a little before, when Rene d'Anjou was king of rebellious Catalans then at war with Ferdinand's father. When the civil war ended in the defeat of the Catalans, Columbus fled Catalonia and for a time served in the French navy under Admiral Guillaume de Cazenove Coullon. After participating in a battle between the fleet of Cazenove and four merchant ships of Genoa off Cape Saint Vincent in 1476, he settled in Portugal.<sup>56</sup>

Many Portuguese fought on the Catalan side in the war of 1462 to 1472, including Peter of Portugal, close relative of the Portuguese king who was one of several claimants of the crown of Catalonia-Aragon. Columbus' intimacy with the Portuguese court, like his marriage to a Portuguese noblewoman (Filipa Monis Perestrello), would have been inconceivable were he not from a socially prominent family and had he not had prior contact with the Portuguese nobility, as for example, in Catalonia during the war of 1462-1472.

#### Comment

*Dr. Philip A. Mackowiak:* Are a patient's age, family history, socioeconomic status, religious background, and ethnicity clinically relevant? One might just as well ask, is there anything in a patient's history other than his signs and symptoms relevant to the nature or consequences of his illness? If the answer is yes, then questions concerning Columbus' true heritage are potentially as important clinically as they are historically.

For if the Catalan hypothesis is correct, Columbus would have been nearly 50 (not 41) when his arthritis first flared. He would have been the scion of a prominent Catalan family, possibly the son of a converted Sephardic Jew, and not the illiterate wool sorter from Genoa tradition maintains was miraculously transformed into one of the greatest mariners of the Age of Discovery. Moreover, if he had come from the vicinity of Barcelona, as suggested by the evidence presented above, rather than from Genoa, as purported in the standard account, he would have

been nearly twice as likely to have had the HLA-B27 genotype so tightly linked to the severest cases of reactive arthritis (Figure 1).

Five hundred years have passed since the death of Columbus on May 20, 1506, and the cause of his arthritis has yet to be determined. If the bones now residing in Santo Domingo or Seville were to be identified conclusively as his,<sup>2</sup> subjecting them to molecular examination for syphilis and HLA-B27 might help solve the mystery of the cause of his arthritis. However, for the time being, we must accept the fact that the disease responsible for Columbus' years of intense suffering and death, like the true identity of his birth place, remains a secret that refuses to be told.

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