coracoid. Zimmer may be credited, however, with the observation (based on external measurements from a flying crow) that the dorsal ends of the coracoids diverge during downstroke.

8. Each wing in a starling was calculated to generate about 0.5 N of centrifugal force; this calculation is based on data from amputated wings (each weighing 4.95 g) of a 78-g starling that were quick frozen in an extended position. From this preparation the centers of mass and gyration were determined to be 3.2 and 3.6 cm, respectively, from the shoulder joint (C. Ellington and S. A. Rasmussen, personal communication).
9. Birds were implanted with markers in both acrocoracoids as in (*2*). Excursions of the furcula were determined from films taken in dorsoventral projection before intubation and compared with a similar analysis undertaken after intubation.
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Symmetrical Erosive Peripheral Polyarthritis in the Late Archaic Period of Alabama

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Rheumatoid arthritis was first described unambiguously in 1800, but its etiology and historical origins are still obscure. Definite rheumatoid arthritis has not been demonstrated in pre-19th century Old World skeletal remains. Six individuals who lived 3000 to 5000 years ago in northwestern Alabama and present erosive polyarthritis characteristic of rheumatoid arthritis are described. The diagnosis raises the possibility that rheumatoid arthritis can be associated with a New World pathogen or allergen.

RHEUMATOID ARTHRITIS, FIRST recognized in Europe, appears to be a relatively new disease (*1*). Except for Sydenham's (*2*) ambiguous description, Landre-Beauvais (*3*) provided the earliest documentation of rheumatoid arthritis in 1800, followed by Charcot's (*4*) in 1853 and Garrod's (*5*) in 1859. Published assertions of rheumatoid arthritis in skeletons antedating 1800 describe lesions or patterns of lesions that are not characteristic only of rheumatoid arthritis, being instead even more characteristic of osteoarthritis or spondyloarthropathies (*6–13*). We describe six prehistoric native Americans, each exhibiting a pathological pattern consisting of the presence of several kinds of lesions accompanied by the absence of several other kinds of lesions, all arranged in a particular anatomical distribution; rheumatoid arthritis is characterized by this pattern.

We examined skeletons of 84 adults who lived during the Late Archaic Culture Period, 3000 to 5000 years ago, along 19 miles of the Tennessee River immediately below Florence, Alabama. Each skeleton is directly or stratigraphically associated with distinctive Late Archaic artifacts. The excellent bone preservation derives from interment in acid-neutralizing mussel shell middens at Late Archaic riverine encampments.

While investigating paleopathologies in this group, we discovered lesions in six skeletons corresponding to lesions noted in contemporary rheumatoid arthritis patients. Although the consistent anatomic distribution of lesions in six individuals contraindicates postmortem artifact, we examined each lesion (magnification to ×40) for post-mortem artifact (pseudolesion). Four of the six affected individuals are female and two are male. Two (including one male) died at ages between 30 and 40 years, two (including the

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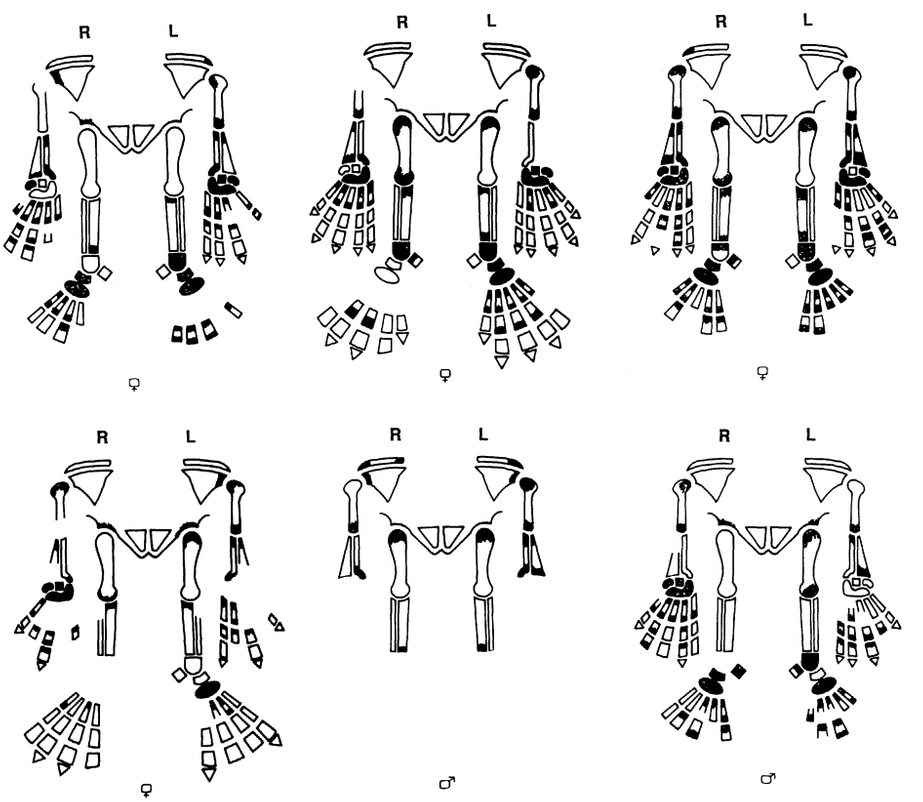

Fig. 1. Homunculi illustrating skeletal distribution of erosive lesions in individual Late Archaic native Americans. Nonvisualization of a bone indicates missing skeletal material, except for the spine and sacroiliac joints. Spine and sacroiliac joints, though present in all skeletons portrayed, contained no evidence of erosion or fusion.

second male) between 35 and 45 years, one between 40 and 50 years, and one between 50 and 70 years.

These six individuals present polyarticular antemortem lytic lesions, distributed symmetrically among appendicular, primarily peripheral, joints, and without vertebral syndesmophytes, sacroiliac lesions, or evidence of reactive inflammatory responses. Diarthrodial involvement is extensive (Figs. 1 and 2), predominantly and evenly affecting hands and feet, frequently including carpals, most severe at metacarpophalangeal, metatarsophalangeal, and proximal interphalangeal joints, and minimally involving distal interphalangeal joints. Two of the six second cervical vertebrae display mild odontoid erosion. Neither squaring nor syndesmophytes occur among vertebral centra; zygoapophyseal vertebral and sacroiliac joints are normal. Enthesial remodeling, bony ankylosis, and periosteal reaction are absent. Osteophytosis is minimal or absent at all diarthrodial joints, including those with erosive lesions. Eburnation with secondary osteoarthritis occurs at one knee. Several phalanges of hands exhibit distal juxta-articular cortical depressions corresponding to pressure erosions from extensor surface subcutaneous nodules (*14*).

Radiographically (Fig. 3), marginal erosions predominate, bordered with no or minimal reactive sclerosis. The term "marginal" here refers to the bare area of bone within the synovial membrane-lined space, extrinsic to cartilage-covered (subchondral) bone. Even those lytic lesions that grossly exhibit nearly continuous bony floors produce no radiographic evidence of condensed or sclerotic borders. These floors must be poorly mineralized, since radiographs of live subjects do not resolve bone density variations involving less than 30 to 50% of bone mineral content (*12, 13*). No subchondral sclerosis occurs. Periarticular osteopenia characterizes all six individuals.

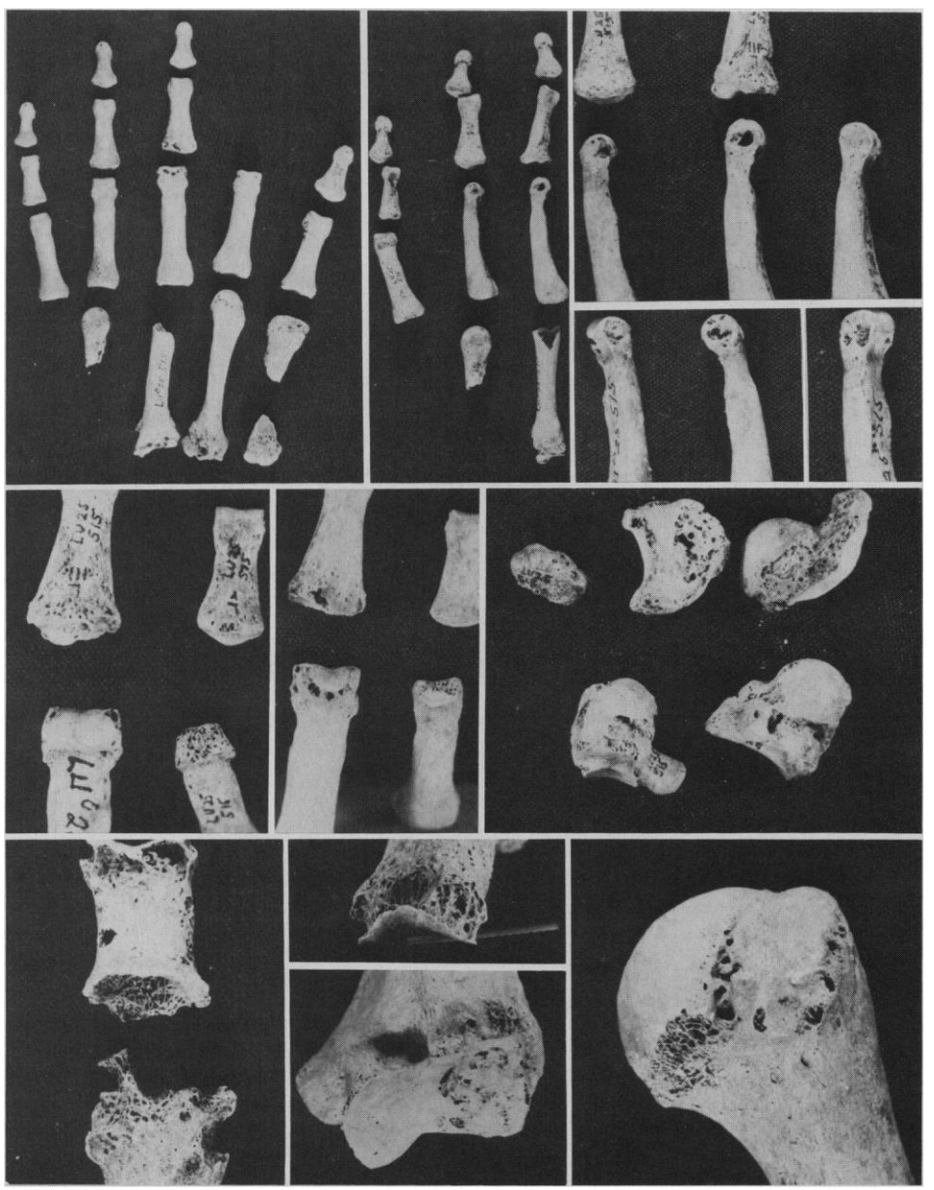

Fig. 2. Photograph of representative examples of erosive involvement in affected Late Archaic skeletons. Note erosive lesions with fronts of resorption associated with loss of subchondral trabeculation and minimal new bone formation.

The constellation of gross and radiographic attributes described above is distinct to rheumatoid arthritis (*11–13, 15–19, 21*). Involvement of nearly every diarthrodial joint, seen in two of the six affected individuals, may occur in individuals with other arthritides, yet not as a frequent phenomenon in any population. Morphologically, the erosive lesions themselves are unlike nonrheumatoid arthritic lesions in contemporary patients' skeletons (*12, 13*), but markedly like those found in macerated rheumatoid specimens among 3000 contemporary skeletons in the Todd Collection (*20*) and in macerated rheumatoid specimens from contemporary patients (*21*). The only spinal involvement in the six individuals occurs as two instances of odontoid disease, found in nearly one-fourth of contemporary rheumatoid arthritis patients. Periarticular osteopenia occurs in about half of spondyloarthropathic patients, almost all patients with active rheumatoid arthritis, and all six of the affected Late Archaic individuals.

Erosive joint disease in spondyloarthropathies (ankylosing spondylitis, psoriatic arthritis, Reiter's syndrome, and bowel-disease associated arthritis) is, for almost all affected individuals, asymmetric and pauciarticular with periostitic or enthesial reaction, bony ankylosis, and occasional sclerosis (*7, 8, 10–12, 15, 22*). Psoriatic arthritis also presents more interphalangeal than metacarpophalangeal involvement, erosion of distal phalangeal tufts, infrequent carpal involvement, frequent axial involvement, and less frequent osteopenia (*11, 18, 22, 23*). Polyarticular infectious arthritis, rare in this typically monoarticular disease, presents perilesional reactive periostosis or osteomyelitic foci (*7, 8, 11*).

In radiographs, advanced polyarticular gout exhibits perierosional reactive sclerosis, additional reactive bone formation, and the overhanging edge sign (*7, 11, 18*); some excavated English skeletons even retain gouty tophi (*9*). Pseudogout (calcium pyrophosphate deposition disease) is typically not associated with periarticular osteopenia, but with chondrocalcinosis, giant geodes (cysts), flattened sclerotic metacarpal heads, osteoarthritis, and eburnation (*11, 16*). Erosive osteoarthritis, distinguished by associat-

Table 1. Joint involvements among arthritic contemporary patients (*25*) and arthritic Late Archaic individuals expressed as percentages of afflicted groups with involvement of specified joints as indicated by gross (clinical) examination, radiographic assessment, and technetium polyphosphonate nuclide scan.

Joint or joint complex	Exam type	Individuals with (%) joint involvement			Joint or joint complex	Exam type	Individuals with (%) joint involvement		
		Rheumatoid patients	Late Archaic individuals	Spondyloarthropathy patients			Rheumatoid patients	Late Archaic individuals	Spondyloarthropathy patients
Shoulder	Gross	46	83	9	Knee	Gross	82	83	23
	Rad.	7–26	17	21		Rad.	21–42	40	8
	Scan	46		41		Scan	78		36
Elbow	Gross	66	83	41	Ankle	Gross	54	83	36
	Rad.	14–39	34	9		Rad.	2–22	0	8
	Scan	78		45		Scan	74		59
Wrist	Gross	92	100	50	Intertarsal	Gross	34	80	14
	Rad.	42–65	40	17		Rad.	14–42	20	8
	Scan	98		64		Scan	68		55
Metacarpophalangeal	Gross	70	100	35	Tarsometatarsal	Gross	26	100	9
	Rad.	39–59	40	13		Rad.	36	20	13
	Scan	70		49		Scan	66		50
Hand: proximal interphalangeal	Gross	40	80	23	Metatarsophalangeal	Gross	70	100	25
	Rad.	42–56	40	20		Rad.	35–49	40	18
	Scan	48		30		Scan	41		18
Hand: distal interphalangeal	Gross	8	20	7	Foot: interphalangeal	Gross	2	80	10
	Rad.	8–10	0	14		Rad.	8–9	20	11
	Scan	17		9		Scan	16		11
Hip	Gross	12	83	9					
	Rad.	2–15	17	17					
	Scan	2		5					

Fig. 3. Radiograph of representative examples of erosive involvement in affected Late Archaic skeletons. Note periarticular osteopenia, "dot dash" (loss of cortical margin definition), and gross erosive changes.

ed osteophytes and subchondral sclerosis, predominately involves interphalangeal joints, occasionally involves first carpometacarpal and first metatarsophalangeal joints, but rarely involves intercarpal or metacarpophalangeal joints (*24*).

The overall pattern of joint involvement (Table 1) in the Late Archaic polyarthritis is strikingly like that in rheumatoid arthritis and not like that in spondyloarthropathies. Joint involvement frequencies in the Late Archaic polyarthritic individuals do not differ significantly ($\chi^2 = 2.6$; $P = 0.05$) from those based on radiographic surveys of contemporary rheumatoid arthritis patients, although involvement frequencies in the prehistoric group are statistically independent of those based on radionuclide scans (*12, 25*). Given the pattern of involvement, lesion morphology, radiological appearance, female predominance, and in view of the differential diagnosis, we conclude that these six Late Archaic individuals are the earliest known sufferers of a disease indistinguishable from rheumatoid arthritis.

The absence of published reports describing equally unambiguous evidence of rheumatoid arthritis in the Old World before 1800 and the presence of an indistinguishable arthritis in the precontact New World

suggest that the disease may have originated in the New World and entered the Old World after 1492 but before 1785. We further propose that rheumatoid arthritis may derive from pathogens or allergens originally native to the New World. This interpretation is more parsimonious than the alternative of a parallel, independent evolution of a now-extinct unknown New World polyarthritis which also produced a constellation of osseous attributes distinct to rheumatoid arthritis.

Items present in both the Late Archaic lifeway and the Colonial period transatlantic trade are potential agents of transportation of this disease. Our consideration of the Late Archaic lifeway and of the temporal and geographic patterns of early transatlantic trade (*26*) implicates tobacco, deer, people, rodents, and dogs as most likely to be associated with a vector, pathogen, or allergen responsible for rheumatoid arthritis.

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Antiproliferative Activity of a Hybrid Protein Between Interferon-γ and Tumor Necrosis Factor–β

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A hybrid protein between interferon-γ and tumor necrosis factor–β was made by ligating the respective genes and expressing the fused genes under the control of the *trp* promoter in *Escherichia coli*. The antiproliferative activity of the hybrid protein in vitro was greatly increased compared with either interferon-γ or tumor necrosis factor–β alone, and both antiviral activity and cytotoxic effect were retained in the hybrid protein. The hybrid protein may have potential clinical application.

COMBINED TREATMENT OF TUMOR cells with tumor necrosis factors (TNFs) and interferons (IFNs) has resulted in a synergistic anticellular effect in many cases (*1–5*). In some tumor cell lines, growth inhibition only occurs after treatment with a combination of both lymphokines (*3, 5*). Synergism between IFNs and TNFs has been observed even in a TNF-resistant tumor cell variant (*6*). On the basis of these observations we constructed two plasmids in which the IFN-γ and TNF-β (lymphotoxin) genes were juxtaposed so that they would form a possible fusion protein under the control of the *Escherichia coli trp* promoter. We report here that one of these constructs expresses a hybrid protein with both IFN-γ and TNF-β activity, and this protein has a greater antiproliferative effect on the tumor cell line ME-180 in vitro than either lymphokine alone.

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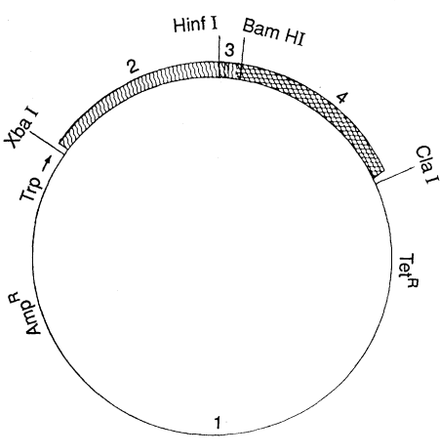

Fig. 1. Plasmid structure for IFN-γ–TNF-β fusion protein expression. Region 1, 4660-bp Xba I–Cla I vector fragment from pγ143 (*18*); region 2, 406-bp Xba I–Hinf I fragment coding for IFN-γ from pγ143 (*18*); region 3, synthetic DNA to link and fuse coding region; region 4, 597-bp Bam HI–Cla I fragment coding for TNF-β from pLT *trp*-1 (*17*). The two plasmids differ in the synthetic DNA fragment region used to link the two coding regions. Plasmid pγTNF-β1 contains the synthetic sequence AGT CAG ATG CAC TCA ACT CTG AAG CCA GCA GCA CAC CTG ATC GGG, and therefore codes for the first 134 residues for IFN-γ (*7*) and the last 148 residues of TNF-β (*5*). Plasmid pγTNF-β2 contains additional 27 nucleotides (CTG TTT CGA GGT CGA AGA GCA TCC CAG) between base 9 and base 10 of the above sequence. Consequently, pγTNF-β2 codes for the entire length (143 residues) of human IFN-γ fused to the 148 residues of TNF-β.