Chronic Non-Hematogenous Osteomyelitis Treated with Adjuvant Hyperbaric Oxygen*

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ABSTRACT: **Between 1979 and 1982, thirty-eight patients with chronic non-hematogenous osteomyelitis were treated by local débridements of the wound, prolonged parenteral administration of antibiotics, and an average of forty-eight once-a-day treatments with hyperbaric oxygen. Of these thirty-eight patients, thirty-four remained free of clinical signs of osteomyelitis for an average of thirty-four months (range, twenty-four to fifty-nine months) after this regimen of treatment. Only four of the thirty-eight patients had been free of clinical signs of osteomyelitis for as long as three months during the two years preceding this treatment. Three of the four failures of treatment were evident within one month after treatment. This method of treatment appears to prolong the infection-free interval of patients with chronic non-hematogenous osteomyelitis.**

For more than two decades, it has been evident that therapy with systemic hyperbaric oxygen as an adjuvant to débridement of the infectious focus in bone, as well as systemic administration of antibiotics, is helpful in the treatment of chronic osteomyelitis. One of us (J. C. Davis) recently reported[11] the results of a follow-up evaluation of forty patients who were treated with the regimen just described and who were first studied in 1979[38]. Most of the patients were military personnel who had had either a gunshot or war wound or an open fracture. Thirty-four of the forty patients remained free of infection after a length of follow-up ranging from twelve to fifty-three months, while six had a recurrent infection. Of the patients with a longer follow-up (range, 7.5 to 10.5 years), thirty of thirty-four remained free of infection while four had additional relapses at intervals of two to six years. Thus, 75 per cent (thirty of forty) of the original patients remained free of infection. In the present report, a similar group of thirty-eight patients who were treated from 1979 to 1982, with similar results, is described.

The osteomyelitis that originates by non-hematogenous spread from a contiguous focus of infection secondary to trauma or surgery has a predilection to become chronic. Chronic osteomyelitis originating in that way has been defined as a bone infection that persists for more than six weeks after the initiating episode, with persistently exposed bone, continued drainage, and positive culture of material taken from the bone[36]. The recommendations for treatment have included the following, in various combinations: multiple débridements, prolonged courses of antibiotics[50,51], prolonged irrigation of the wound and perfusion with antibiotic solutions or detergents[8,25], systemic administration of hyperbaric oxygen[2,10,12,15,38,41,47], and implantation of antibiotic-impregnated beads into the wound[26]. In addition, bone grafts have been suggested to fill dead space and to treat associated non-union[40,43] as well as muscle transposition flaps[14,49] and free muscle flaps with microvascular techniques[34,37] when there is exposed bone.

Despite treatment by the methods just mentioned, some patients have continued to have chronic osteomyelitis[48]. What constitutes so-called adequate surgical and antibiotic treatment is a matter of considerable controversy.

One feature that has been common to all reports of regimens of treatment for chronic osteomyelitis is the absence of controls in the clinical studies. The many variables that exist in the case of each patient make it virtually impossible to conduct a controlled study. Therefore, the evaluation of each regimen must be based on each patient serving as his or her own historical control[1], and the duration of the disease-free period (freedom from pain, local redness, and drainage) after treatment must be the measure of success or failure. Under these circumstances, one must include a long-term follow-up of results in the study, because often a good initial short-term successful result does not stand the test of time. A recurrence of infection may lead to repeated hospitalizations and repeated operations, with changes in the antibiotics that are used. All of these factors have to be considered in evaluating a regimen of treatment as to effectiveness and cost.

Materials and Methods (Table I)

From November 1, 1979, to November 1, 1982, thirty-eight patients with chronic non-hematogenous osteomyelitis were treated by a regimen[38] that included débridements of the wound, parenteral administration of antibiotics to which

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the infective organisms were sensitive, and repeated daily adjunctive administration of hyperbaric oxygen. The diagnosis was definite in each patient. The history, the results of the physical examination, and the appearance of the radiographs were typical, and a positive culture of material from the bone was recorded for all thirty-eight patients. For inclusion in this study, the patient had to meet the following previously defined criteria[38]: the infection had been present for at least six months, the patient had had at least one surgical procedure designed to eliminate the infection, the patient had been treated previously with parenteral antibiotics, and the patient was available for an evaluation at a minimum of two years after our regimen of treatment.

TABLE I

CHARACTERISTICS OF THE STUDY GROUP

	No. of Patients
Total	38
Male	24
Female	14
Age	
<31 yrs.	14
31-40 yrs.	9
41-50 yrs.	4
51-60 yrs.	5
>60 yrs.	6
Duration of infection	
6 mos.-1 yr.	14
1-5 yrs.	13
6-10 yrs.	2
≥11 yrs.	9
Infection followed:	
Open fracture	20 (53%)
Closed fracture	8 (21%)
Abscess or infection of a joint or at the site of a prosthesis	10 (26%)
No. of previous surgical procedures	
1	11
2	8
3-5	2
6+	7
"Multiple"	10
Average length of follow-up	34 mos. (range, 24 to 59 mos.)

Duration and Prior Treatment

Twenty-four patients were male and fourteen, female. The average age at the time of treatment was forty years, with a range from sixteen to seventy-six years. The average duration of osteomyelitis was 8.9 years, with a range from six months to fifty years. The average number of surgical procedures for osteomyelitis in twenty-eight patients was 6.1. The remaining ten patients reported having had multiple surgical procedures; however, the exact number could not be determined. The previous surgical procedures included débridement in all of the patients, and all had been treated with parenteral antibiotics. All of the thirty-eight patients had an actively draining wound at the time when treatment was initiated. One patient had insulin-dependent diabetes mellitus and another had severe rheumatoid arthritis. The other thirty-six patients had no significant associated disease. The thirty-eight patients in the present series, who were drawn totally from a civilian population, were similar to the forty patients in the series of Morrey et al.[38], who were drawn largely from a military population.

The longest period of absence of drainage from the wound in thirty-four of the thirty-eight patients in the last two years before treatment was three months.

Etiology and Site of Involvement

Twenty patients had had an open fracture, including four who had had massive destruction of tissue and bone by a gunshot or bomb. Ten had had a contiguous abscess or articular infection. Eight had had a closed fracture that was treated by open reduction and internal fixation. No patient had hematogenous osteomyelitis. The most common area of involvement, in nine patients, was at the site of a fracture of the distal tibial or fibular diaphysis.

Microbiology

Aerobic and anaerobic cultures of material taken from the involved bone at the time of débridement were grown, and bacteria were retrieved from all thirty-eight patients. A single microorganism was recovered from thirty-three patients. *Staphylococcus aureus* was the single pathogen in seventeen patients; *Pseudomonas aeruginosa*, in eight patients; *Proteus mirabilis*, in two patients; *Serratia marcescens*, in two patients; *Escherichia coli*, in two patients; and *Enterobacter cloacae* and *Staphylococcus epidermidis*, in one patient each. In five patients, multiple microorganisms were found: these infections were combinations of *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Enterobacter cloacae*, *Serratia marcescens*, and *Escherichia coli*.

Treatment

A medical team consisting of an orthopaedic surgeon, a specialist in infectious diseases, and a physician with a specialty in hyperbaric medicine was involved in the application of the regimen for each patient. While one of us (J. C. Davis) was involved in the case of every patient, a total of thirteen orthopaedic surgeons and specialists in infectious diseases applied the regimen in this series of patients. In the initial débridement, all dead bone, sclerotic bone, foreign bodies, and sinus tracts were removed. Daily treatment with hyperbaric oxygen was begun on the first postoperative day. As soon as data on the sensitivity to antibiotics of the retrieved microorganism or microorganisms were available, an appropriate parenteral antibiotic was administered. The dosage was determined by the specialist in infectious diseases, according to professional recommendations at the time of treatment. Six days a week, each patient was brought to the hyperbaric chamber. Care of the wound was provided by the same physician each time, who evaluated all wounds daily and coordinated any needed formal surgical débridement under anesthesia in the

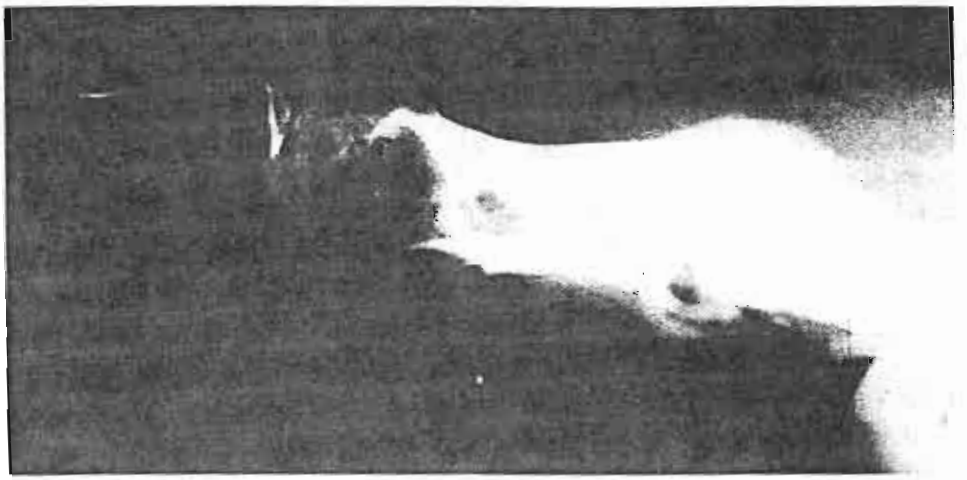

FIG. 1-A

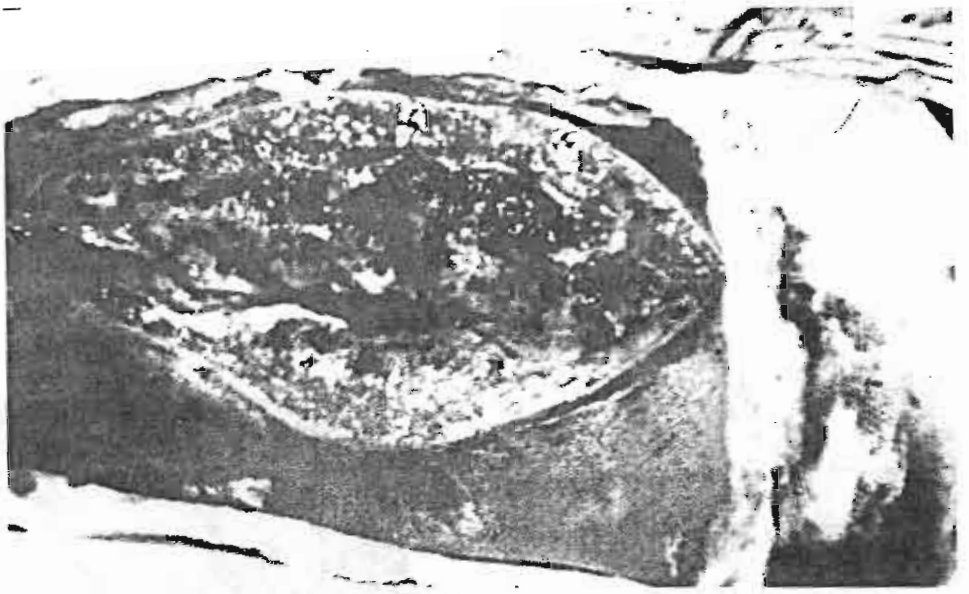

FIG. 1-B

FIG. 1-C

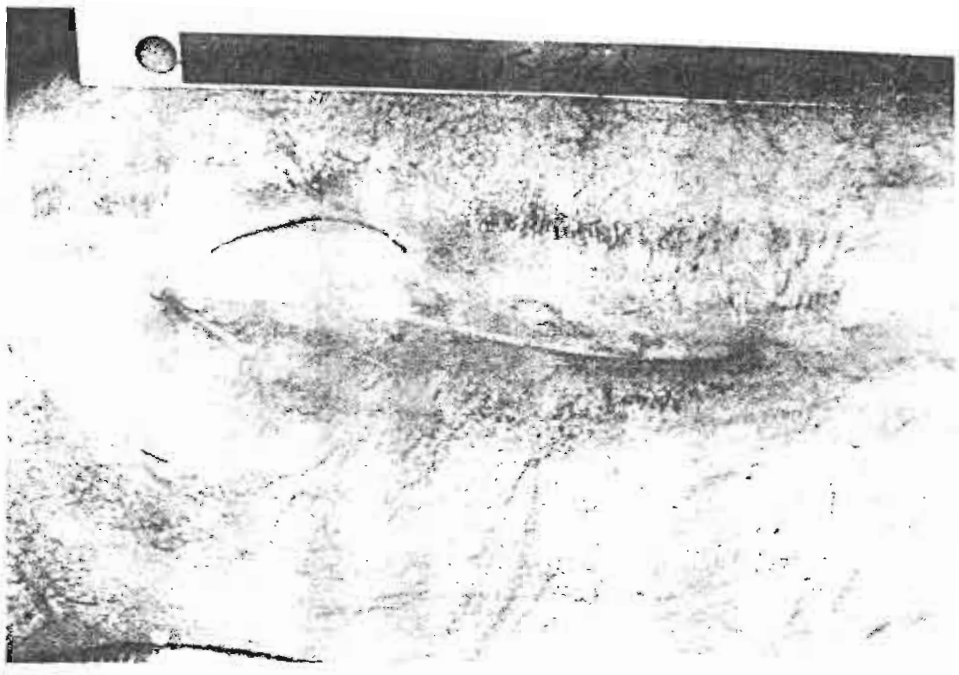

FIG. 1-D

Figs. 1-A through 1-E: This infection and non-union of the femur persisted at seventeen months after fracture despite two débridements with plate fixation, one autogenous bone graft, and parenteral administration of antibiotics for Pseudomonas osteomyelitis.

Fig. 1-A: Radiograph made immediately after removal of the plate, screws, and sequestra.

Fig. 1-B: The wound was packed open.

Fig. 1-C: After fifty-eight treatments with hyperbaric oxygen, the limb was clinically stable and the bone was covered with healthy granulation tissue. A walking cast was applied.

Fig. 1-D: At one-year follow-up, there was solid osseous union, with no signs of infection.

operating room. Surgical débridement was performed whenever purulent drainage or necrotic bone appeared in the wound. Twenty-six patients required more than one formal débridement in the operating room. Irrigation with sterile saline solution and light débridement were performed daily, and all wounds were packed lightly with gauze that had been soaked in 0.125 per cent acetic acid in order to suppress superficial growth of *Pseudomonas aeruginosa*.

In the hyperbaric chamber, the patient was first exposed to compressed air that was raised to a pressure of 2.4 atmospheres absolute. Humidified 100 per cent oxygen was supplied at thirty-five liters per minute through a head-tent that was taped around the patient's shoulders, with exhaust to the outside of the chamber. This high rate of flow ensured inhalation of 100 per cent oxygen and avoided accumulation of carbon dioxide. Sampling of oxygen inside the head-tent during each treatment documented the inspiration of 100 per cent oxygen. Measurements of arterial blood gas under these conditions demonstrated arterial oxygen tensions of 1,100 to 1,300 millimeters of mercury, depending on the patient's pulmonary status.

Each day's treatment with hyperbaric oxygen comprised ninety minutes of breathing oxygen, using a schedule of three thirty-minute periods of breathing oxygen, interrupted by ten-minute periods with the hood open for breathing air from the chamber environment as a precaution against pulmonary oxygen toxicity[17].

The thirty-eight patients received an average of forty-eight daily treatments (range, eight to 103) with hyperbaric oxygen for a total of 1,816 treatments. Treatments with

FIG. 1-E

At four-year follow-up, the patient had no signs of infection.

hyperbaric oxygen were continued as long as the bone was not fully covered with healthy vascular tissue. Three patients required tympanotomy tubes to allow equilibration of the pressure in the middle ear during changes of the pressure in the chamber. The other thirty-five patients were able to inflate the middle ear by themselves without difficulty. Two patients reported changes in visual acuity toward myopia during treatment. Both patients regained normal visual acuity by six to eight weeks after treatment was completed.

The individual surgeon made a decision on any reconstructive procedure according to the size and location of the residual wound and the over-all clinical status of the patient. In twenty patients the wound was left open to heal secondarily. Autogenous bone-grafting was done in fourteen patients and coverage with a rotational muscle flap, in four.

During the four years comprising this series, there were no significant trends or changes in the antibiotics that were used. The following antibiotics were used alone or in combination and were selected according to the results of cultures of specimens of bone that were taken at operation and the sensitivities of the microorganisms: gentamicin, vancomycin, tobramycin, piperacillin, amikacin, cefoperazone, netilmicin, oxacillin, ticarcillin, cephalothin, mezlocillin, cefazolin, cefamandole, cefoxitin, moxalactam, trimethoprim, clindamycin, and sulfamethoxazole.

Dosages were managed by specialists in infectious diseases to maintain blood levels within therapeutic ranges. The duration of parenteral treatment with antibiotics ranged from three to six weeks, and some patients completed the course with intravenous therapy on an outpatient basis.

Results

The patients were followed for an average of thirty-four months (range, twenty-four to fifty-nine months) after completion of the treatment protocol. During this period, thirty-four patients remained clinically free of infection. To be termed free of infection a patient had to have a healed wound with no drainage, no tenderness or pain, and no cellulitis. The thirty-four patients with a successful result had received an average of forty-five treatments (range, eighteen to 103) of hyperbaric oxygen and required an average of thirty-two days (range, zero to 103) of hospitalization.

The goals of adjuvant treatment with hyperbaric oxygen differed for the thirty-eight patients. Eleven of the sixteen patients with an infection at the site of a non-union had healing without bone-grafting but with débridement, antibiotics, and hyperbaric oxygen to help to control infection and promote capillary angiogenesis. The remaining five patients with a non-union had healing with autogenous bone grafts after preparation with hyperbaric oxygen. In nine patients without non-union who had a successful result, autogenous bone-grafting was used to obliterate dead space after preparation with hyperbaric oxygen. In twenty patients (including the eleven patients with a non-union), the goal of treatment with hyperbaric oxygen was to promote healthy granulation in wounds that were left open to heal secondarily. Eighteen of these wounds remained healed du follow-up, and two patients had continued drainage. goal of treatment with hyperbaric oxygen in the remai four patients was to help to prepare a recipient bed coverage with a muscle flap in three and to cover expo bone in one in whom coverage with a partial flap fai Two of these four patients had a recurrence at one mo and six months. Thus, of twenty wounds that were left o to fill with granulation tissue, eighteen healed. All four patients who had autogenous bone grafts after prepara with hyperbaric oxygen had healing, and two of the f who underwent coverage with a muscle flap before or a treatment with hyperbaric oxygen had healing. Figures 1 through 1-E illustrate the case of one patient with an infec non-union who was treated with débridement, antibioti and hyperbaric oxygen without bone-grafting. Data on t four patients in whom the treatment failed will be discuss

All of the seventeen patients in whom *Staphylococc aureus* was the single pathogen remained free of recurren during the follow-up period, as did the five patients wi infection from a mixture of pathogens. The seventeen pa tients who had an infection with *Staphylococcus aureu* received an average of forty-two treatments (range, eighteen to seventy-six) of hyperbaric oxygen, were hospitalized fo an average of twenty-seven days (range, zero to seventy-five), and required an average of 1.4 débridements as par of the treatment protocol. The five patients who had an infection with a combination of pathogens received an average of forty-seven treatments (range, twenty-seven to ninety) of hyperbaric oxygen, were hospitalized for an average of thirty-three days (range, zero to sixty), and required an average of two débridements.

Treatment of three of the eight patients who had an infection with *Pseudomonas aeruginosa* and the one who had an infection with *Escherichia coli* (all had gram-negative organisms) failed (Table II). The five patients who had an infection with *Pseudomonas aeruginosa* and who had a successful result received an average of sixty-eight treatments (range, forty-one to 103) with hyperbaric oxygen, were hospitalized for an average of forty-nine days (range, ten to 103), and required an average of four débridements.

Failures of Treatment

Table II is a summary of the data on the four patients in whom the treatment failed. Of the three patients who had an infection with *Pseudomonas aeruginosa*, in two the wound never ceased to drain and in one, drainage recurred at one month. In the patient who had an infection with *Escherichia coli*, drainage recurred at six months.

Case Reports

CASE 1. This patient had sustained open fractures of the tibia and fibula eleven months before entering the study. During that time he had been hospitalized almost continuously for treatment by multiple débridements, prolonged parenteral administration of antibiotics, and attempts to cover exposed bone with rotational and cross-leg flaps. When a four-centimeter area of the tibia was exposed and drainage continued, treatment

TABLE II

ANALYSIS OF THE PATIENTS IN WHOM THE TREATMENT FAILED

	Case 1	Case 2	Case 3	Case 4
Age (*yrs.*)	38	49	63	29
Sex	M	F	M	F
Duration of infection	11 mos.	24 mos.	45 yrs.	12 yrs.
Status	Exposed bone	Draining	Draining	Exposed bone
Etiology	Open fracture	Septic arthritis, severe rheumatoid arthritis	Open fracture	Infected decubitus ulcer
Underlying disease	None	Rheumatoid arthritis	None	None
Site	Mid. part of tibia	Head of humerus	Distal part of tibia	Ischium
Organism	*P. aeruginosa*	*P. aeruginosa*	*P. aeruginosa*	*E. coli*
Surgery	Débridement, myocutaneous flap (shortly before treatment with hyperbaric oxygen)	Débridement	Débridement	Débridement, myocutaneous flap
No. of treatments with hyperbaric oxygen	99	44	33	31
Time to recurrence	1 mo.	Continued drainage	Continued drainage	6 mos.
Final outcome	Pathological fracture, below-the-knee amputation	Continued drainage	Continued drainage	Recurrent drainage in opposite hip

with hyperbaric oxygen was begun on an outpatient basis as part of our standard protocol. By the twelfth treatment with hyperbaric oxygen, surrounding healthy granulation tissue was closing the defect and growing through drill-holes. With daily improvement, we continued hyperbaric oxygen without formal débridement, and after ninety-nine treatments the defect was almost totally covered; hence, all treatment was stopped. One month later the patient sustained a pathological fracture at the site, and a below-the-knee amputation was elected.

CASE 2. A forty-nine-year old woman had a long-standing history of severe rheumatoid arthritis. The pain and the drainage from the osteomyelitis of the shoulder had not responded to repeated débridements and antibiotic treatment for two years before she entered the study. After débridement and five treatments with hyperbaric oxygen, the pain and drainage decreased. After twenty treatments, she was discharged from the hospital, and during the next twenty-four treatments with hyperbaric oxygen and daily changes of dressing on an outpatient basis, she became free of pain, but drainage persisted.

CASE 3. This patient had sustained a fracture of the distal end of the tibia in 1930. Drainage from the area of the osteomyelitis began in 1935 but cleared spontaneously. It recurred after eighteen years of latency, and during the twenty-seven years before our treatment drainage was persistent despite prolonged courses of parenteral antibiotics, débridements, and skin-grafting. Plain radiographs and tomograms showed a large destructive lesion in the distal end of the tibia but no definable sequestrum. Surgical treatment consisted of excision of the sinus tract and débridement of a large area of infected bone. Histological examination showed focal areas of inflammation that were consistent with chronic osteomyelitis. The patient refused plans for autogenous bone-grafting and continued treatment with hyperbaric oxygen and antibiotics for the large defect, which was lined with healthy granulation tissue. Examination at the two-year follow-up revealed that the defect never closed completely and was again draining.

CASE 4. This woman had been paraplegic since sustaining a spinal cord injury at the age of seventeen years. A decubitus ulcer at the ischium that had started at that time recurred repeatedly, despite reconstruction with multiple flaps and finally disarticulation of the right hip. (She is the only patient in the series with osteomyelitis that was caused by a decubitus ulcer.) She continued to hold a job and drive an automobile between admissions for surgical procedures during a twelve-year period, but infection and drainage were nearly continuous. On admission to this study, plain radiographs and bone scans showed osteomyelitis of the right ischium, and a sinus tract was found to extend to the ischium. After eighteen preoperative treatments with hyperbaric oxygen, resection of the decubitus ulcer, subtotal resection of the ischium, and reconstruction with a flap were performed. After thirteen postoperative treatments with hyperbaric oxygen, the wound had healed and she was discharged from the hospital. Six months later she had pain and drainage from the left ischial region. Although the right side remained healed, the result was a failure.

Discussion

Infected bone and the associated soft-tissue wounds are hypoxic[15,21,22,33,38,42,44,46]. Parts of the infected wound may be subject to reduced blood flow despite a demonstrated high consumption of oxygen[39,46]. This hypoxia interferes with several cellular functions in the infected wound. First, the proliferation of fibroblasts and the production of collagen to support capillary angiogenesis are impaired[4,20,45]. Second, although leukocytes migrate into relatively ischemic and hypoxic tissue[24], oxidative killing of bacteria by the leukocytes is impaired by hypoxia. Elevation of the oxygen tension in the wound to a normal or above-normal level[3,9,17-19,22,24,27,32,33] enhances the bactericidal potential of the leukocytes.

After hemoglobin is fully saturated with oxygen, 2.2 volumes per cent of oxygen will physically dissolve in blood for each atmosphere of pressure of hyperbaric oxygen in the chamber. Therefore, a total of 5.2 volumes per cent will be dissolved at 2.4 atmospheres. When it is administered within established safety limits[5-7,30], hyperbaric oxygen at more than 1,100 millimeters of mercury provides arterial

oxygen tensions to plasma and interstitial fluid, so that the oxygen tension in partially ischemic, infected, hypoxic wounds of bone and soft tissue[13,32,33] can reach that level. Moreover, steep gradients[42] from hyperoxia to hypoxia in these wounds provide the stimulus that is needed for macrophages to produce the angiogenesis factor[23,28,29].

It is virtually impossible to compare the results in the reports on various techniques of treatment of chronic osteomyelitis. Some of the variables include the criteria for diagnosis (duration of infection, bacteriology, and so on), the type of osteomyelitis (hematogenous or non-hematogenous), the extent of the involvement, the vascular status of the extremity, and the duration of follow-up. Nevertheless, the results in our thirty-eight patients are encouraging. Thirty-four of the thirty-eight patients were free of drainage, pain, and local or systemic signs of infection and had not needed repeat hospitalization for a minimum of two years.

In one patient (Case 1) who had a failed result, we failed to follow our protocol. Coverage of dead bone with healthy tissue does not replace complete débridement and bone-grafting, if needed, for structural integrity. From the outset the goal of treatment of another patient (Case 2) who had a failed result was palliation, and she had relief of pain in the shoulder and a lessening of drainage. Cure by any method was not considered possible in this patient because she had severe rheumatoid arthritis. The third patient (Case 3) who had a failed result did not accept the full protocol that would have required bone-grafting to fill the large defect, prolonged administration of antibiotics, and treatment with hyperbaric oxygen. The fourth patient (Case 4) had either a new focus or an extension from the original focus of osteomyelitis in the opposite ischium.

While two of the four patients in whom treatment failed might have had a successful result with the complete protocol, we must admit that some of the patients with a successful result might have had healing without the adjuvant treatment with hyperbaric oxygen. However, the goal of treatment in nineteen patients in this series who had involvement of the tibia was to salvage the limb; most of the limbs were destined for amputation if our treatment failed. There was only one amputation in this series.

We are aware that there are weaknesses in the prese study, including the following. The absence of medical re ords prevented precise documentation of the adequacy previous treatments. No claim can be made regarding cu of the disease, because such a claim would require a long follow-up. This is why we used the concept of the infectio free interval as a measure of success. Also, there we important variables, such as the location, duration, and s verity of the infection and the vascular status of the affecte part. However, our study demonstrated a decrease in mo bidity as reflected by the length of the intervals that t patients were free from infection at follow-up.

The side effects of hyperbaric oxygen were minimum Although we noted changes in visual acuity in two patien in our series, a study by Lyne[31] showed no structural chang in the eyes of twenty-six patients who underwent daily trea ments with hyperbaric oxygen. There were no episodes in dicating toxicity from hyperbaric oxygen to the pulmonar or central nervous system.

We wish to emphasize that the therapy with hyperbari oxygen cannot be given sole credit for the results in ou patients. The daily débridements and meticulous care of the wound by experienced physicians and the use of culture-specific antibiotics played a large role in prolonging the disease-free intervals in our patients. However, the fact that all but four of these thirty-eight patients with chronic non-hematogenous osteomyelitis remained free from infection for twenty-four months or longer cannot be overemphasized. We believe that hyperbaric oxygen played a significant role by alteration of the wound dynamics, as discussed.

Finally, in spite of these encouraging results and similarly encouraging results in a previous series of patients[10,38], we are careful not to regard our patients as cured of the chronic osteomyelitis. A much longer follow-up than that used in the present report is essential before a true rate of cure can be determined. However, the excellent long-term results[11] that have been achieved (a disease-free interval ranging from 7.5 to 10.5 years in thirty of forty patients) may well be considered a cure. We believe that it was the combined treatment protocol, not any one of its components, that was responsible for the reported successful results.

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