Polyarteritis Nodosa

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CASE PRESENTATION

A 30-year-old man was referred for evaluation and treatment of Still disease. His illness had begun 12 years earlier when, as a high school senior, he developed daily temperatures of 38.4°C to 38.9°C. Following an extensive evaluation, he was given the diagnosis of Still disease (systemic-onset juvenile rheumatoid arthritis) and treated with indomethacin. Indomethacin helped control the fevers, which resolved after approximately 1 year. However, 3 years later, the fevers returned. He was hospitalized on several occasions after developing temperatures that were as high as 40.0°C and responded only to high doses of corticosteroids. The patient started a prednisone regimen that he continued for the next 8 years, with frequent attempts to taper his dose on an alternate-day basis. Despite the prednisone, 1 year later the patient began to develop purple toes, digital tissue loss, and foot ulcers (Figure 1A-B).

Until the onset of his problem at 18 years of age, the patient was in good health. Since starting prednisone treatment, however, he had developed posterior subcapsular cataracts, osteoporosis, and mild glucose intolerance. At his evaluation, his prednisone dose was 40 mg/d alternating with 16 mg/d. On the days that he took the lower steroid dose, he experienced fevers. To control the pain from his ulcers, he took up to 9 tablets of acetaminophen with codeine each day. His other medications included etodolac (400 mg twice daily), pentoxyfylline (400 mg 3 times/d), alendronate (10 mg/d), trimethoprim-sulfamethoxazole DS (3 times a week), dapsone (25 mg/d), acetylsalicylic acid (325 mg/d), and several vitamins and supplements. At age 30, he was taking an average of 28 pills a day.

The patient had been married for 3 years at the time of his presentation. He and his wife had been attempting to conceive a child for approximately 12 months, without success. The patient worked as a school librarian and did not smoke or drink. His family medical history was noncontributory. The review of systems was remarkable for a diffuse, lacy discoloration of the skin. Some months before his evaluation, the patient had undergone biopsies of his skin, sural nerve, and gastrocnemius muscle that revealed vasculitis of medium-sized arteries with fibrinoid necrosis (Figure 2).

As the patient walked to the examining room, he was observed to have a foot-slapping gait caused by a left foot drop. On examination, he was afebrile and normotensive and had a normal respiratory rate, but his resting pulse was 138/min. He had a cushingoid face and a so-called buffalo hump at the junction of his shoulders and neck. He had truncal obesity and purple striae over the skin of his abdomen and flanks and the medial section of his knees. There was generalized livedo reticularis over his skin (including his face), a large, well-healed scar from a previous ulcer over his left medial malleolus, several active ulcerations on the dorsal surfaces of his feet, and significant digital pulp loss in several toes of the left foot. Motor strength testing revealed weakness of the left foot flexors.

Laboratory testing was remarkable for a white blood cell count of 28 700 × 10³/µL, a hematocrit level of 33.7%, and a platelet count of 285 000 × 10³/µL. The patient’s serum creatinine level was 1.0 mg/dL (88 µmol/L), and his urinalysis showed 1+ protein but no cells. The erythrocyte sedimentation rate was 40 mm/h. As-
say results for antinuclear antibodies and anticardiolipin antibodies were negative. The result of the Russell viper venom test was 35.1 seconds (normal: 27.0-45.0 seconds), and a rapid plasma reagin test was nonreactive. Results of a serum immunofluorescence assay for antineutrophil cytoplasmic antibodies (ANCA) were negative, as were test results for hepatitis B and C. A chest radiograph revealed no abnormalities.

**DISCUSSION**

**Diagnostic Impression**

Still disease was first described in 1897 by George Still, a London physician who entitled his original treatise “On a Form of Chronic Joint Disease in Children.” Still observed that the disease nearly always began “before the second dentition,” but an adult form of the condition was described in 1971. Quotidian fevers, one of the hallmarks of Still disease, characteristically occur with high temperature spikes followed by defervescence within hours. Eighty percent of patients have temperatures of at least 40°C during these febrile episodes. Our patient’s fevers, which frequently fit this pattern, were the principal reason for believing that Still disease might be the correct diagnosis. However, several other features of the patient’s illness suggested an alternative explanation.

Ninety-five percent of patients with adult-onset Still disease have arthritis within 1 year of presentation. In contrast, our patient had never experienced arthritis at any point in his course. The patient also had no lymphadenopathy, pharyngitis, splenomegaly, or serositis, other features of the disorder described by Still. Patients with Still disease often present with a rash: a fine, evanescent, salmon-colored eruption that demonstrates a predilection for the proximal limbs and trunk. Our patient’s livedo reticularis and lower extremity ulcers were distinctly different from the typical Still disease rash. In short, the patient’s skin lesions, clinical evidence of a mononeuropathy (the foot drop), and vasculitis of medium-sized arteries suggested another explanation for the cause of the patient’s illness: polyarteritis nodosa (PAN).

**First Case**

In the inaugural volume of the *Deutsches Archiv für Klinische Medizin* (*German Archive for Clinical Medicine*), Adolf Kussmaul and Rudolf Maier reported the case of a 27-year-old journeyman tailor named Carl Seufarth. Although they were not the first to report a patient with features of PAN, Kussmaul, an internist, and Maier, a pathologist, were the first to recognize the constellation of findings as a new clinical entity. Seufarth’s illness had begun perhaps several months earlier but proceeded swiftly to death during his 30-day hospitalization in Freiburg, Germany. Recounting the case, Kussmaul and Maier wrote that Seufarth was “[o]ne of these patients for whom one can already give the prognosis before the diagnosis. The first impression was of a lost soul whose... days were numbered. . . . “

Seufarth, who had felt unwell for at least 1 month before presentation, was febrile (38.2°C) and tachycardic on admission. Throughout his hospitalization, he experienced intermittent fevers (as high as 39.2°C), and his pulse ranged from 112 to 140/min. He “climbed up the two tall flights of stairs to the internal medicine clinic without assistance . . . [but] felt so weak that
he immediately had to go to bed.” He complained of 1 day of numbness on the volar aspect of the thumb and the 2 neighboring fingers of the right hand. Throughout the ensuing days, this minor neurological deficit grew more pronounced: “Already in the next days the general weakness increased so rapidly that he was unable to leave the bed, [and] the feeling of numbness also appeared in the left hand.” The muscle paralysis progressed quickly but at an inconsistent rate. It “accelerated for one or more days, and then on the following days seemed to improve again... but such improvements were not stable and soon things were worse than ever.” The overall effect was devastating: “Before our eyes, a young man developed a general paralysis of the voluntary muscles.... [He] had to be fed by attendants, and within a few weeks was robbed of the use of most of his muscles.” In the entire medical literature, there may be no more vivid description of a rapidly advancing mononeuritis multiplex.

With the limited therapeutic armamentarium of his day, Kussmaul could do little more than wonder about the patient’s inexorable decline. He puzzled over the patient’s condition and documented the clinical deterioration carefully. “On May 30th... pea-sized nodules were discovered in the subcutaneous skin of the abdomen and chest. ...” Kussmaul excluded 1 common malady of the day—trichinosis—because the subcutaneous nodules were atypical of that disease, as were the overt indications of Bright disease (inflammation within the kidneys).8 Seufarth’s death was described poignantly: “On June 2nd, the patient was in a state of extreme weakness. He was scarcely able to speak, lay with persistent severe abdominal and muscle pains, opisthotonically stretched, whimpering, and begged the doctors not to leave him. Death occurred on June 3rd at 2 o’clock in the morning.”

At autopsy, visible nodules were present along medium-sized arteries (FIGURE 3A-B): “One glimpse of the transected muscles... immediately demonstrated something unusual. Namely... numerous, whitish small tumors up to the size of poppy seeds and hemp seeds.” The localization of inflammation to the perivascular sheaths as well as to the media and outer layers of the arterial walls, combined with the nodular thickening over blood vessels, led Kussmaul and Maier to suggest the name periarteritis nodosa.

**Naming Polyarteritis Nodosa**

For decades after the description of this first case of PAN, most forms of vasculitis were termed periarteritis nodosa. Newly recognized types of this disease were characterized and classified according to features similar to or distinct from those of PAN.9,10 For example, early cases of what became known as Kawasaki disease were labeled *infantile periarteritis nodosa* because aneurysms within the coronary arteries in that disease are similar to the lesions of PAN.11,12 In the early 1900s, Ferrari13 and Dickson14 proposed the name *polyarteritis nodosa*, partly to distinguish the disorder described by Kussmaul and Maier4 from the vascular lesion of tertiary syphilis. Furthermore, the term *polyarteritis nodosa* emphasized the panarteritic nature of this disease and underscored the fact that multiple arteries are affected by the process.15

**Epidemiology**

Studies of the epidemiology of PAN have been hampered by the disease’s evolving definition through the decades. Wohlwill16 was the first to detect a variant of PAN in which glomeruli (small blood vessels, ie, differentiated capillaries) were involved prominently. In 1948, Davson et al17 suggested dividing PAN patients into 2 groups according to the presence or absence of glomerulonephritis. One group of patients, Davson and colleagues noted, demonstrated renal vasculitis only in medium-sized vessels of
the kidneys (sparing the glomerulus). We now refer to disease such as this group had as classic PAN. In contrast, patients in the other group had glomerular inflammation with or without medium-sized vessel involvement, a disease subset designated microscopic PAN. More recently, microscopic PAN has been renamed microscopic polyangiitis in recognition of its tendency to involve not only arteries but also capillaries and veins. The frequent occurrence of ANCA in patients with microscopic polyangiitis suggests that this disease differs from classic PAN not only pathologically but also perhaps etiologically. Because of changes in the definition of PAN, many early studies of this disease’s epidemiology included patients with microscopic polyangiitis and probably other diseases as well.

The 1994 Chapel Hill Consensus Conference on the nomenclature of systemic vasculitides defined classic PAN as necrotizing inflammation of medium-sized or small arteries that spares the smallest blood vessels (arterioles, venules, and capillaries) and is not associated with glomerulonephritis. Under this strict definition, classic PAN is believed to be rare. From 1988 to 1994, not a single case of classic PAN was reported by the Norwich Health Authority (England), which serves an area with a population of more than 400000. Most other reported annual incidence rates have ranged from 2 to 9 cases per million annually. PAN appears to affect men and women with approximately equal frequencies and to occur in all ethnic groups. The highest reported incidence rate of the disease, 77 cases per million, occurred in an area hyperendemic for hepatitis B virus (HBV) infections. With the availability of the HBV vaccine, the number of cases associated with this viral infection have declined substantially. Hepatitis B virus now probably accounts for less than 10% of all cases of PAN in the developed world (L. Guillemin, oral communication, May 2002).

**Clinical Features**

PAN typically develops subacutely, with the onset of constitutional symptoms over weeks to months. Many of the initial symptoms of PAN are recognized only in retrospect, once the diagnosis has been established. Fevers, a common feature at diagnosis, rarely occur in such prominent isolation as in our patient. The characteristics of fever in PAN vary from one patient to another, ranging from intermittent, low-grade fevers (as Seufarth experienced) to high fevers with chills (as our patient occasionally experienced). Malaise, fatigue, weight loss, and myalgias are also common in PAN. Arthralgias of large joints (knees, ankles, elbows, and wrists) occur in up to 50% of patients, but true synovitis occurs in only a minority.

Vasculitis of medium-sized arteries usually produces 1 of 4 cutaneous findings, all of which may occur in the same patient: livedo reticularis, nodules, ulcerations, and digital ischemia. Any event leading to disordered blood flow through medium-sized arteries (eg, cold or vasospasm) can cause a livedoid pattern of skin discoloration. However, the livedo reticularis caused by active vasculitis does not blanch upon pressure. Nodules and ulcers tend to occur on the lower extremities, particularly near the malleoli and in the fleshy parts of the calf. Nodules frequently evolve into ulcerations with scalloped borders. Although nodular lesions are the clinical finding from which the name periarthritis nodosa was derived, they are in fact probably the least common cutaneous manifestation of this disease. Medium-sized arteries lie within the deep dermis and in the adipose tissue below the skin. Thus, the diagnosis of PAN can be made by skin biopsies of nodules or ulcer edges that are sufficiently deep to capture lobules of subcutaneous fat. Digital ischemia, often accompanied by splinter hemorrhages, sometimes leads to tissue loss.

Mononeuritis multiplex, the infarction of named nerves (eg, the sural, peroneal, radial, or ulnar nerves), occurs in approximately 60% of patients with PAN. In vasculitis, mononeuritis multiplex results from inflammation in the vasa nervorum. Vasculitic neuropathy tends to involve the longest (ie, distal) nerves first and usually begins asymmetrically. For example, our patient presented with a left foot drop; Seufarth’s hand complaints first involved the right hand and then the left. In advanced stages, the neuropathy may mimic a confluent, symmetrical polyneuropathy, but a careful history taking may unmask its initial asymmetry.

Nerve conduction studies detect the typical axonal pattern of nerve injury and identify involved nerves for biopsy. The sural nerve, which mediates sensory perception but not motor function, is the one that most commonly undergoes biopsy. Because muscle tissue is highly vascular and may harbor involved vessels even in the absence of symptoms or signs (such as an elevated serum creatine kinase level), biopsies of the gastrocnemius muscle should be performed simultaneously. Alternatively, biopsies of the superficial peroneal nerve and the peroneus brevis muscle may be performed. Advanced mononeuritis multiplex can be an enormously disabling problem from which recuperation is measured in months or years, if at all. Residual nerve dysfunction in the form of muscle weakness or painful neuropathy is common. The patient’s degree of recovery is difficult to predict.

The gastrointestinal manifestations of PAN (Figure 4) occur in approximately half of all patients. These symptoms are among the most challenging to diagnose correctly because of their nonspecific nature and the requirement for either mesenteric angiography or surgical exploration. Postprandial abdominal pain (intestinal angina) is common. Either mesenteric infarction or aneurysmal rupture in PAN is a disastrous complication of mesenteric artery involvement by PAN, with high mortality rates. Angiography of the mesenteric (and renal) vessels (Figure 4B) reveals multiple microaneurysms, ranging in size from lesions that are barely visible to those large enough to rupture on occasion. Sometimes PAN is detected at cholecystectomy or appendectomy in the absence of other disease manifestations. In such cases, surgical removal of the involved organ is sometimes curative.
Intraparenchymal renal inflammation is a major feature of PAN, found in 40% of patients. Because of the disease’s predilection for medium-sized, muscular arteries, the inflammatory process targets the renal and interlobar arteries, occasionally involving the smaller arcuate and interlobular arteries as well but sparing the glomeruli. The primary renal manifestations of PAN are microaneurysms within the kidney, large wedge-shaped renal infarctions that are visible on cross-sectional imaging studies, and mild to moderate renin-mediated hypertension. Proteinuria and hematuria are common on urinalyses, but red blood cell casts are exceptional because they indicate glomerulonephritis.

Tachycardia is common and often striking in PAN, as both our patient and Seufarth illustrate. Specific heart lesions are rarely diagnosed during life, but autopsy series indicate cardiac involvement in a majority of patients. Seufarth’s epicardial arteries resembled the pathological appearance of arteries at other sites: “The left anterior descending coronary artery and several branches of the right coronary artery...[were] almost entirely thickened to misshapened [sic], nodular, white-yellowish cords” (Figure 3B). Patchy necrosis of the myocardium caused by subclinical arteriolar involvement is a frequent finding. Congestive heart failure and myocardial infarction sometimes result.

With less regularity, PAN may involve a host of other organs, including the brain, eyes, pancreas, testicles, ureters, breasts, and ovaries. However, for reasons that are not understood, PAN spares the lungs. The occurrence of pulmonary lesions (pulmonary nodules, cavities, infarcts, or alveolar hemorrhage) in systemic vasculitis shifts the differential diagnosis in favor of vasculitides commonly associated with ANCA (Wegener granulomatosis, microscopic polyangiitis, and the Churg-Strauss syndrome), antiglomerular basement membrane disease (Goodpasture disease), and other disorders.

Serology
Assays for antinuclear antibodies and rheumatoid factor are also generally negative in PAN, albeit low nonspecific titers of these antibodies may be detected. Patients with HBV-associated PAN are generally hypocomplementemic, regardless of whether they have demonstrable cryoglobulins. The erythrocyte sedimentation rate and C-reactive protein are often useful in longitudinal evaluations of disease activity but are nonspecific and do not correlate well with the presence or absence of active disease in all patients. The sera of some patients with PAN are positive for ANCA when tested by immunoﬂuorescence (ie, showing either a cytoplasmic or perinuclear pattern of immunoﬂuorescence, more commonly perinuclear). However, specific enzyme immunoassays for antibodies to proteinase-3 or myeloperoxidase (the 2 antigens known to be associated with systemic vasculitis) are negative in classic PAN. Positive enzyme immunoassays for antibodies to these specific antigens are much more consistent with Wegener granulomatosis, microscopic polyangiitis, or the Churg-Strauss syndrome.

Pathology
PAN has a striking tendency to involve medium-sized muscular arteries. It spares the aorta and its major branches, as well as capillaries and small arterioles that lack muscular coats. In contrast to many other forms of vasculitis, PAN also spares the venous system (Figure 5). Although Kussmaul and Maier termed the disorder periarteritis nodosa, the site of the earliest lesion in PAN remains a matter of debate (J. Jenette, oral communication, April 2002) even 150 years after the first unequivocal case description. Because of the tendency of PAN to involve branch points, it is conceivable that the earliest lesion occurs in the intima.
Acute lesions swiftly evolve into a panarteritis with degeneration of the arterial wall, various amounts of destruction of the external and internal elastic lamina, and fibrinoid necrosis. The cellular infiltrate is pleomorphic, with both polymorphonuclear cells and lymphocytes present in various degrees at different stages. Degranulation of neutrophils within and around the arterial wall leads to leukocytoclasis. In time, this inflammation leads to transmural necrosis. The vascular wall inflammation in PAN may be strikingly segmental, affecting only part of the circumference of a given artery (Figure 5). Segmental necrosis, in turn, leads to aneurysm formation. During later stages, complete occlusion may occur secondary to endothelial proliferation and thrombosis. Throughout involved tissues, the coexistence of acute and healed lesions is typical. Features of granulomatous vasculitis are absent. Acute PAN evolves into a sclerotic process with fibrosis of the damaged arterial wall and mesenchymal organization. In some cases, there is also recanalization of thrombi.

Chronic arterial narrowing may result. Hepatitis B virus–associated PAN appears to be an immune complex–mediated disease. The virus’s surface antigen and antibody complexes are present in the circulation. Deposits of HBV surface antigen, immunoglobulin, and complement are found in the vasculitic lesions of muscular arteries, dermal capillaries, glomeruli, and vasa nervorum. Serum complement levels are low during periods of active HBV-associated PAN, consistent with complement consumption by immune complex deposition. In contrast to that of PAN cases associated with HBV, the role of immune complexes in the pathophysiology of idiopathic PAN, if any, remains unclear.

**Etiology and Immunopathogenesis**

The final sentence of the report by Kussmaul and Maier reads: “We would only like to add that we looked for syphilis in Seufarth during his life and after death, but without any positive result.” Thus, the authors of the original case description strongly suspected an infection as the cause of their patient’s condition. Indeed, they mistook the “countless small nodules” found at autopsy for an undeveloped parasite. After the publication of an initial report that an infestation of nematodes had caused the disease, Kussmaul and Maier later recanted this assertion, likely with some embarrassment.

The association of some cases of PAN with HBV infection was first described in 1970. PAN develops early in the course of HBV infection, usually within the first 6 months, and is therefore usually the first indication of an HBV infection. Serum hepatic transaminase levels may be normal in up to 50% of cases associated with HBV. Seroconversion from hepatitis B e antigen positivity to the production of anti–hepatitis B e antibodies usually signals recovery. Liver biopsies in HBV-associated cases of PAN show chronic hepatitis. Numerous other infectious agents have been implicated in PAN and other forms of systemic vasculitis (including streptococcal infections in childhood PAN), but consistent proof of a role for any specific microbial pathogen in causing classic PAN remains absent.

**Treatment**

For cases of idiopathic PAN, corticosteroids and cytotoxic agents remain the cornerstones of treatment. Approximately half of patients with PAN achieve remissions or cures with high doses of corticosteroids alone. Cyclophosphamide (eg, 2 mg/kg orally each day, or 0.6 g/m² intravenously every month, decreased in the setting of renal dysfunction) is indicated for patients whose disease is refractory to corticosteroids or who have serious involvement of major organs. The Five Factor Score has been used to delineate which patients would benefit from cyclophosphamide therapy from the outset of treatment. It was developed in a cohort of 336 patients with either polyarteritis nodosa or Churg-Strauss syndrome. Five clinical features were associated with mortality: gastrointestinal bleeding, perforation, infection, or pancreatitis; renal insufficiency (serum creatinine level...
>1.58 mg/dL [139.7 µmol/L]); proteinuria higher than 1 g/d; involvement of the central nervous system; and cardiomyopathy. Each of these factors carries an added risk of mortality of approximately 10%. Developers of the score have suggested that patients with Five Factor Scores of 0 might be treated effectively without cyclophosphamide but that the presence of any of these 5 factors associated with a poor prognosis should lead to the consideration of cyclophosphamide treatment. Treatment of HBV-associated PAN with immunosuppressive agents has deleterious long-term effects on the liver. Fortunately, the availability of effective antiviral agents has revolutionized the treatment of HBV-associated cases in recent years. One effective strategy involves the initial use of prednisone (1 mg/kg per day) to suppress the inflammation. Patients begin 6-week courses of plasma exchange (approximately 3 changes per week) simultaneously with corticosteroids. At age 30 years, he had already undergone bilateral cataract surgery. Clearly, his condition required cyclophosphamide. Because of his and his wife’s ongoing efforts to conceive a child and concerns about the possibility of infertility with cyclophosphamide use, the patient froze sperm samples before undertaking this therapy. By the time he had made arrangements for sperm banking and returned for treatment 2 months later, he had developed several deep skin ulcerations and a new right foot drop.

At the start of cyclophosphamide therapy (2 mg/kg per day), the patient’s daily prednisone dose was increased to 40 mg (the alternate-day corticosteroid taper was abandoned). Albeit effective for some forms of inflammation, alternate-day corticosteroid regimens are less effective in vasculitis. The patient also began taking 1 single-strength tablet of trimethoprim-sulfamethoxazole daily as prophylaxis against Pneumocystis carinii pneumonia. Finally, his complete blood cell count was checked every 2 weeks, with the intention of keeping his white blood cell count at least 4000 × 10^3/µL.

Because of his previously refractory disease, the prednisone was tapered slowly. By 6 months, he had tapered his daily dose of prednisone from 40 mg to 15 mg, with healing of his ulcers for the first time in years. He was able to discontinue all of his pain medications. Ten months after starting cyclophosphamide treatment, the patient and his wife celebrated the birth of a daughter, conceived through in vitro fertilization. Shortly thereafter, he tapered off prednisone for the first time in a decade. Cyclophosphamide was discontinued after 10 months and replaced with azathioprine (2 mg/kg per day) for 1 year. Now, 8 months after discontinuing azathioprine, he remains in remission despite receiving no treatment. The risk of relapse is believed to be low, although it may be higher than the rate observed in cases associated with HBV (<10%).

CONCLUSIONS

This case contains 2 major lessons for physicians. First, in general terms, one should be wary of clinging firmly to a diagnosis (in this case, Still disease) based purely on nonspecific features such as fever. In the absence of symptoms, signs, or other findings that are pathognomonic for any particular illness, the physician must continually reevaluate the diagnostic information available, even while proceeding with what appears to be the appropriate therapy. From complex clinical scenarios, features of a specific disease may emerge in time, permitting more precise diagnoses and offering new avenues for therapy. In this case, the skin lesions, foot drop, and biopsy-proven vasculitis of medium-sized muscular arteries cast the patient’s fever pattern in a new light and led to the specific diagnosis of PAN.

Second, many physicians and physicians-in-training view PAN as an invariably chronic illness with universally toxic treatments. On the contrary, this case illustrates that with careful treatment, close follow-up, and the rigorous use of measures designed to prevent common complications of treatment (eg, frequent blood cell count checks and Pneumocystis carinii prophylaxis), patients with PAN may achieve excellent outcomes. Former recommendations for the use of cyclophosphamide in treating systemic vasculitis included the continuation of the medication for 1 full year after the achievement of disease remission. Albeit effective in inducing disease remissions, such regimens led to prolonged treatment courses and a host of drug-induced adverse effects. Currently, even as investigators seek more specific and less toxic treatments for vasculitis, the use of shorter courses of cyclophosphamide may optimize the effectiveness of this drug while minimizing its potential adverse effects. In this case, the careful use of cyclophosphamide put a disease that had been refractory for more than 10 years into a medication-free remission.
The man who discovers a new scientific truth has previously had to smash to atoms almost everything he had learnt, and arrives at the new truth with hands bloodstained from the slaughter of a thousand platitudes.

—José Ortega y Gasset (1883-1955)