The following is the second in a 3-part series on the history and contemporary use of sclerotherapy. Read part one online at PracticalDermatology.com.

H. I. Biegeleisen, a talented and versatile phlebologist, may have unknowingly become the father of cosmetic phlebology when he authored, in 1935, the first published article describing purely cosmetic sclerotherapy for the treatment of telangiectasia associated with varicose veins. He used tiny self-fabricated needles of his own design, which permitted him to cannulate telangiectasias.

If current trends continue, the number of phlebological procedures carried out for cosmetic purposes may exceed those carried out for treatment of vascular diseases. Without receiving credit for it, H.I. Biegeleisen’s son, Kenneth, may have been the first person to employ cyanoacrylate adhesives to treat varicose veins over 30 years ago (personal communication).

MOLECULAR PHARMACEUTICALS

Proteomic studies, which have identified both the signaling systems and genes whose activations are responsible for both normal and pathophysiologic biologic events, have resulted in the synthesis of pharmaceuticals that operate at the molecular level. To paraphrase Gary S. Wood, we now have the molecular tools to put pathologic disorders in their true biological context and develop truly curative therapies.

HYPOXIA AND PATHOLOGIC ANGIOGENESIS

Responses to low oxygen concentrations at the cellular level are mediated by transcriptional agents such as hypoxia inducible factors (HIFs), which are signaling compounds responsible for upregulating more than 70 genes, which modulate proangiogenic pathways. The direct transcriptional target of these signaling pathways is vascular endothelial growth factor (VEGF), the principle regulator of angiogenesis. Manipulation of the HIF pathway will provide therapeutic benefits for a wide variety of pathological entities including solid tumors, which rely on angiogenesis for growth and metastasis, as well as ischemic heart disease, peripheral artery disease, and wound healing. For phlebologists, the manipulation of these pathways will have important implications for the control of venous disease.

AMINAPHTONE VS. ENDO THELIN-1 (ET-1)

Pleiotropic cytokine-like proteins designated as endothelins are secreted by endothelium and upregulated in a variety of pathologic states. ET-1 is the most potent vasoconstrictor yet discovered. Its secretion is upregulated by hyperglycemia, producing ischemic changes resulting in angiogenesis and fibrosis. It is implicated as an etiologic agent in the development of diabetic retinopathy and glomerulopathies caused by the proliferation of pathologic vasculature. Aminaphtone, a derivative of 4-aminobenzoic acid down regulates ET-1 production in vitro by interfering with the transcription of the prepro-ET-1 gene, reducing both vasoconstrictive induced hypoxia, as well as fibrosis by downregulating adhesion molecules. Aminaphtone has also been found useful for the treatment of pulmonary hypertension, certain cardiac abnormalities, and migrainoid visual symptomatology.

“Unlike many of our European and Australian colleagues who have embraced and accredited phlebology for over 60 years, phlebology has never achieved the status of a fully recognized specialty in the US.”
Rapamycin, a modulator of intracellular signaling, has been used successfully for the topical treatment of laser-induced neovascularization, following the treatment of hemangiomas. Employed orally, rapamycin has been proven effective for the treatment of Kaposi’s sarcoma. When it becomes less expensive, and appropriate studies are carried out, it may prove useful for the treatment of unwanted vasculature in a wider variety of settings. Following completion of necessary studies and a reduction in cost, topical rapamycin may become useful for the treatment of lower extremity venous disease in general and unwanted neovascularization in particular.

REPROGRAMMING THE GENOME

Endonucleases, enzymes that produce double stranded breaks in DNA, can be targeted to excise DNA at a specific site in the genome. By activating repair mechanisms, they can introduce desirable changes in the genome. These include knocking out unwanted gene function, or restoring mutated DNA sequences. As noted in a recent article, “Successful genetic editing of one cell primate embryos, will without question, be accompanied by a raft of possible ethical issues.” It also brings us, “One step closer to the potential for manipulating genes in human embryos.”

VASCULAR BIO-PRINTING—ANOTHER BLUEPRINT FOR THE FUTURE

In early 2014, Jennifer Lewis, a Harvard materials researcher, devised a method using bio-printers to create vascularized three-dimensional tissue constructs. She describes the ability to create lab-grown vasculature as a “Foundational step toward creating 3D living tissues.” Dr. Lewis employs 4D printing system, which sequentially dispenses tissue components in the form of biocompatible inks containing Type 1 fibroblasts and Type 2 dermal fibroblasts, derived from human prepuces as well as extracellular matrix. Another ink, designated as pluronic or fugitive, which like the lost-wax process employed by ancient sculptors, is liquefied and evacuated, leaving an interconnected network of “hierarchal hollow branching filaments.” These are then infused with a suspension of human umbilical endothelial cells (HUVECs), which self-replicate and become functional endothelium.

PHLEBOLOGY AMERICAN STYLE

Opportunities and training for phlebologists have evolved quite differently in different parts of the world. Unlike many of our European and Australian colleagues who have embraced and accredited phlebology for over 60 years, phlebology has never achieved the status of a fully recognized specialty in the US.

It seems ironic that the US medical establishment seemingly ignores a pathological process that affects millions of Americans, imposing an enormous burden of suffering and financial costs. As our population ages, the number of Americans afflicted, and the attendant fiscal burdens will expand significantly. There are a number of reasons for this therapeutic gap in the American armamentarium. They include increasingly centralized and restrictive healthcare funding and the intertwined impact of expensive and profitable to use technologies, whose use until recently was exclusive to specific specialties.

ACADEMIC DEFICITS; FINANCIAL BENEFITS

The development of phlebology has not inspired much interest among American academics. Their indifference has resulted in the failure of teaching institutions to provide the resources necessary to develop standardized training programs culminating in certification. Unlike countries where formal training programs are available, aspiring phlebologists here are left with the sole option of finding experienced mentors through various phlebological organizations, from acquaintances, or by training abroad. As a consequence, the treatment of venous disease has been by default “appropriated” by both ambitious physicians and non-physician practitioners, from every conceivable background. Their training and skill levels are manifestly haphazard and sometimes inadequate. Figure 1 demon-

Figure 1. These deep necrotic ulcers followed sclerotherapy carried out by a physician who advertised his skills as a sclerotherapist who mistakenly mixed hypertonic saline with polidocanol. He was totally unaware that the severe pain that prompted agonized complaints from the patient suggested that something untoward and totally unexpected was occurring. Anyone who has ever used polidocanol knows that the injections are essentially painless and that severe pain suggests that something is going horribly wrong.
strategies the risks associated with inadequate training and lack of experience. Technology is sometimes a two-edged sword. As the scope of essential and cosmetic applications expand, cost effective phlebological procedures are rapidly being replaced in the west by expensive, less invasive, and less complication prone technologies. Unfortunately, it is widely suspected that the wholesale employment of these technologies has more to do with financial gain than it does with patient benefits. To further complicate the picture, specialized equipment, particularly imaging technologies, typically “belongs” to the fiercely guarded proprietary and influential provinces of well-established specialties. This setting pits one specialty against another, inevitably provoking attempts to establish jurisdictional monopolies and nasty disputes. In the Third World, the cost of technological “advances” may inhibit continued use of and development of more economical alternatives and impose prohibitive costs.

The profitability theme also resonates among private American medical practitioners, who fear declining incomes as a consequence of both federally sponsored insurance programs and the imposition of network restrictions. Physicians and paramedical personnel with minimal training are incorporating phlebological procedures, often cosmetic in nature, as an antidote for declining revenues. Carelessly written state licensing laws, in the absence of established training requirements, will continue to permit treatment by almost anyone with or without meaningful credentials, occasionally resulting in sometimes-disastrous results. This setting further frustrates the development of American phlebology into a coherent, uniform, and manageable system of treatment. The only people who may continue to be happy with the current state of affairs might be malpractice attorneys.

Ultimately, insurer demands for cost containment may catalyze the development of an American phlebological community. Organizations such as the American Venous Forum (AVF), L’Union Internationale de Phlébologie (UIP –International Union of Phlebology), and The American College of Phlebology (ACP) are more than ready to help establish formal training programs, which will incorporate mandatory curricula followed by certification.

**BARRIERS TO PHLEBOLOGICAL REFORM: SPECIALTY INSULARITY AND XENOPHOBIA**

Advances in every scientific field typically flourish in the context of a cooperative framework of shared information and disparate perspectives. Phlebological progress in particular has always depended upon the cooperative efforts of individuals with diverse backgrounds to devise an eclectic mix of diagnostic and therapeutic algorithms and overcome the fragmentation and specialization of knowledge, which characterize medical and surgical specialties. Extraordinary patient benefits will result from specialty cross-fertilization, and the long overdue dissolution of arbitrary jurisdictional barriers, among what are now antagonistic competitors. The American College of Phlebology, formed in 1986 was composed of multiple specialties, founded by dermatologists, angiologists and vascular surgeons for just this reason. There is concern that over the past 10 years, this organization has been progressively dominated by profit-driven interventional radiologists and others who have attempted to exclude dermatologists and vascular surgeons. Hopefully, consilience and a mutually beneficial and productive equilibrium can be established, which will unite the priorities and values, which currently divide the specialties.

**CLOSE ENCOUNTERS WITH A QUACK – “CONSISTENTLY EXCELLENCE RESULTS”**

In the mid-1980s when there was little to no interest or publications dealing with phlebology, an article appeared describing sclerotherapy in a non-peer reviewed journal written by a mid-western general practitioner. Thinking that it would be worthwhile to communicate with the
rare soul who was actually carrying out sclerotherapy, I sent him a few photographs suggesting that we share experiences. His pecksniffish and meretricious posturing is reprinted verbatim (Figure 2), sans identifying data, per the advice of an attorney.

Needless to say, I was amazed and infuriated by its contents and composed a reply, which in retrospect was more visceral than objective. In it I noted, “I appreciate the candor of your letter, and with equal candor, I must say that if I am prostate for publishing photographs, you sir are a procurer for having 1-800-VEIN in your phone number.” I also pointed out that he appeared to be, “One of those general practitioners who had no specific training,” adding that, “His concerns might have more to do with fear of competition than ensuring patient benefits.” I ended the letter on a more conciliatory note by saying “Perhaps we should stop this invective and cooperate.” Subsequently, colleagues and new patients provided me with copies of his press releases and patient handouts, which were factually untrue and supported by pure bragadocio. In them, he claimed that, “Surgery was obsolete,” “Painful, rather mutilating, always leaving scars involving hospitalization and time off from work.” The recurrence rate was stated to be “85%.” “Other options including electrocautery, laser, and various saline based injections” would, he said, “Burn the skin and leave marks…There is a better way.” His “Exclusive method,” which consisted of nothing more than centuries old sclerotherapy, would “Safely eliminate vein disorders without the scars associated with surgical techniques.” The slogan he employed to describe his method incorporated the word “Cure.” “Varicose veins are gone permanently without surgery or scars, with a 2% recurrence rate.” He then went on to claim that patients were “Treated by licensed M.D.s, specializing in the treatment of vein disease covered by most insurance plans.”

Five years later, I had the opportunity to train a young physician who visited one of the vein clinics after being solicited to join the organization. These verbatim comments were excerpted from his lengthy letter. “Soon after submitting my CV, (the only qualifications were an MD license), I was interviewed by a number of clinic employees...During one of my interviews, a bizarre mission statement emerged...Expand as rapidly as possible into any feasible medical procedure that had a McDonald’s duplicability.” “Speed was thought an essential ingredient, and not missing any window of opportunity which was perceived as another three to five years for sclerotherapy.”

The next goal: “Expand into other franchise medical ventures, hemorrhoid centers, hair transplant clinics, and liposuction outlets.” Most of the employee physicians were, “Semi-retired, burned out, older physicians abandoning previous careers...Minimum revenue must be maintained if the patient count was low,” based on 15 patients per physician daily. “Extensive laboratory evaluations were also performed as a revenue booster.”

His letter also included interviews with his patients who had previously discussed treatment with employees at various vein clinic outlets. Patient #1 met with five employees, “Office personnel, doctors, and financiers.” She was offered “A finance package of monthly payments with 24% annual interest...Each interviewer tried to close the sale.” She was also told that, “Even though she had a few superficial spider veins, they were the result of incompetence of her venous system and would require six to ten $325 treatments.” At the same outlet, a second patient with varicose veins “Received 17 treatments, and spent $5000 and was not finished.” In this case, neither the treating physician or the patient knew exactly what was being injected. The sclerosant employed was represented to the
"Phlebological progress in particular has always depended upon the cooperative efforts of individuals with diverse backgrounds to devise an eclectic mix of diagnostic and therapeutic algorithms and overcome the fragmentation and specialization of knowledge, which characterize medical and surgical specialties. Extraordinary patient benefits will result from specialty cross-fertilization, and the long overdue dissolution of arbitrary jurisdictional barriers, among what are now antagonistic competitors."

As outrage began to percolate through a small group of physician phlebologists, letters were exchanged. Dr. Kenneth Biegeleisen, Dr. David Green, Dr. Gabriel Goren, and I proceeded to file complaints with the Federal Trade Commission, Better Business Bureau, insurance carriers, and the BMQA. Our letters pointed out the glaring inaccuracies in his advertising claims, and the performance of totally unnecessary and very expensive laboratory evaluations on asymptomatic patients. The scandalous nature of the whole operation was so blatant that the National Enquirer published our concerns in May of 1990 (Figure 3). With the passage of time, all of us encountered patients who had received treatments at one of the clinic outlets. We observed tissue necrosis, thrombi, extensive pigmentation, neovascularization, what appeared to be excessive numbers of treatments, expensive and totally unnecessary laboratory evaluations and exorbitant charges.

RES IPSA LOQUITUR

The founder of these vein clinics made unsubstantiated claims that “In 20,000 patients treated no significant complications have occurred.” Unfortunately, complications that occurred at the hands of his employees led to numerous complaints. Documents in one case (Santa Monica Superior court, 1990, WEC-146148), the patient complained of “Severe damage, failed to eradicate varicose veins.”

In another case, a 30-year-old woman developed large ulcers on her legs, and had permanent scarring. Another lawsuit filed in Cook County, IL, MIB: NS #7634, firm code 05620, described a patient who suffered an amputation of her right leg following treatment. In the plaintiff’s complaint, the physicians were noted to have “failed to perform an arteriogram to determine the condition of the patient’s arteries in her legs.” In yet another lawsuit, filed in Cook County, circuit court, "Permanent scarring and ulceration caused the patient to continue to suffer pain and disability as a result thereof."

THE DENOUEMENT

Finally, a combination of FTC injunctions and a barrage of lawsuits may have triggered the disappearance of the medical director and his pernicious enterprise from public view. My understanding is that at least one of the individuals whose name appeared on letterhead is still carrying out phlebological procedures, hopefully unencumbered by ineptitude, catchy slogans, outrageous claims and gross ethical abuses.

This series is adapted from a chapter originally written by Dr. Duffy at the request of a friend and colleague who, unfortunately passed away before the book could be published.

Look for Part 3 to appear in the November and December editions, and for the full series PDF to be posted at PracticalDermatology.com in December.

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