INTEGRATING NEW PRODUCTS & TECHNOLOGIES INTO PRACTICE

NAVIGATING THE BADLANDS OF PROPRIETARY OFFERINGS

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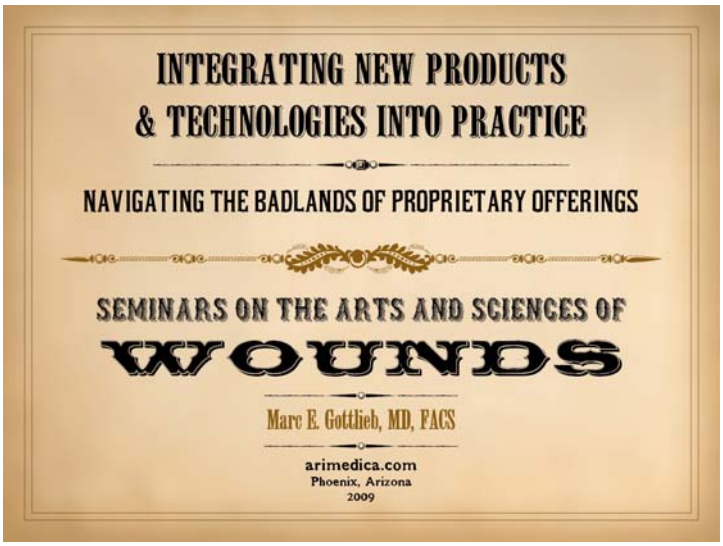

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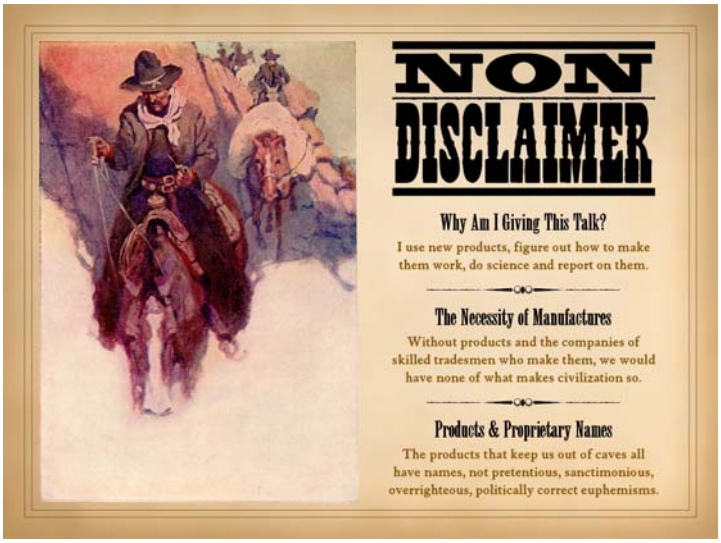
This presentation was first given on September 26, 2009 at the Baptist Health South Florida 4th Annual Wound Symposium. As a new presentation, the organization and flow may seem a bit disjointed and redundant, but sure to improve if I am asked to do this topic again. Nonetheless, the subject is an important one, and hopefully you will find something useful here to help you work your way through the barrage of new products that show up every year.

This is all about to how identify and analyze useful new products. Why? Because all of us want to get the best results for our patients. If your quintessential psyche is more oriented towards people and patients, then you want them to have the best, speediest, most expeditious and trouble free results that they can. If your soul is more focused on the science and techniques, you want your patient projects and scientific investigations to have the best results. Either way, we all want the same thing – the best results – and we are all always looking for the next best thing that gives us the best results. This presentation is all about navigating the ocean of new products.



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Nowadays we seem to live in an environment of phony political correctness and petty pencil pushers who need to tell everyone else what is administratively proper and morally righteous. These are the folks who tell you that accepting a pen or pad of paper from a drug rep is tantamount to the 8th deadly sin and a violation of the 11th biblical commandment. In a society where form has become far more valued than substance, it is assumed that you, the educated professional, are too naive to discriminate legitimate knowledge from hucksterism and proprietary pitches. A presentation can totally suck as long as the presenter has signed a waiver that neither he nor his forebears nor his sire unto the tenth generation has not now nor ever nor ever will own nary a penny share in the stock of those nefarious ne'er-do-wells, the inveiglers of immoral, illegal, illicit, and illegitimate ill-gotten wealth, the fear mongers of medicinal manufactures, the mind-bending minions of the medical-industrial complex, the conspirators of commerce and the corrupters of conscience, the Companies.

Somebody has to speak up for the truth. So, I start this presentation on a thoroughly iconoclastic note. I refuse to make the usual disclaimers. You judge for yourself if what here is of value. Instead, I start with an emphatic NON-disclaimer. **First**, why am I giving this talk? Because I was asked to. This is the last subject in the world I might have thought of giving. But as I pondered how much I would hate preparing this talk, it started to make some sense. Having been through 9 years of surgical residency and 25 years of practice, I have evaluated and used countless new products. I have done my fair share of trials (and errors), and some real science, clinical development, and publication. I guess what I have been good at, and why I work with a variety of companies, is that I have been able to successfully take new products and concepts and figure out what to do with them and how to make them work and integrate them into effective everyday practice.

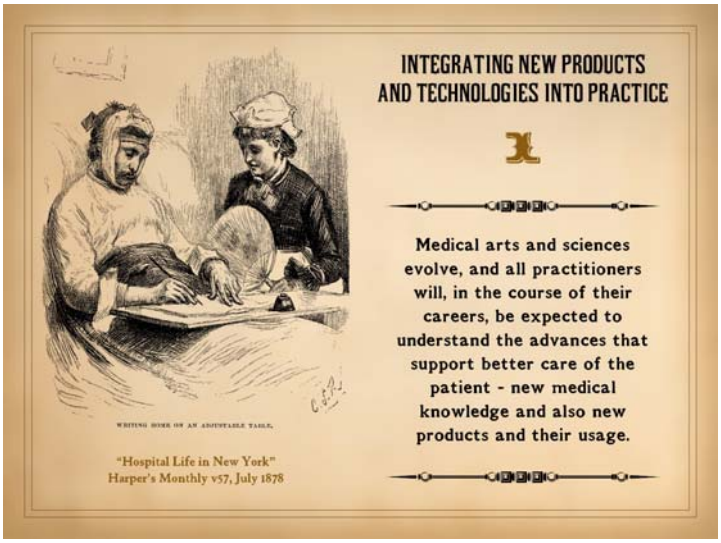
Second, we must mention the necessity of manufactures. Without products and the companies of skilled tradesmen who make them, we would have none of what makes civilization so. It is nice to romanticize about a return to a simpler aboriginal past. Poets and philosophers and artists have done it for ever, but even Henry David Thoreau was able to take Walden Pond for only so long. Imagine a romantic life riding the desert and mountain ranges of the mid 1800's western U.S. You could avoid civilization if you wanted to – but not really. Are you going to walk? Who is to make your boots? You yourself? No problem you say, you will hunt your own animals, prepare your own skins . . . but who is to make your knives and needles? Want to ride the range? Bareback? If you or your horse fancies a blanket, saddle, bridle and tack, who's to make it? Need a rifle? Need a cooking pot? Unless you are ready to renounce all vestiges of civilization and the communities of man and live in a cave, then guess what, you need stuff that someone else made. And vice versa, what you make or do is a necessity for someone else. Our civilization is

predicated on the cooperative specialization and division of labor that makes it possible to have the technical knowledge and skills needed to make things. You can't blow your nose without tissues made by some company. You can't sign those stupid waivers without a pen made by some company (of course, if you are out of tissues, you could leave your mark on the waiver easily enough). Gee, too bad they won't let companies give you a pen anymore so you can sign. We have a civilization. Companies make things. We use them. Medical progress has occurred because of new knowledge and skills, but also because of the devices and technologies that are manufactured to support or implement the knowledge and skills. Not all companies are angelic, but companies and products are not intrinsically evil. It is up to users and prescribers to understand what is of value or not. If the luddites and fuddites ("fud" = fear-uncertainty-doubt) want to return to the trees, good for them. For the rest of us, be responsible and educated about new products, reject the bad, embrace the good, and be neither intimidated nor beguiled by them nor their companies.

Third, we need to acknowledge products and their proprietary names. The products that keep us out of caves all have names, not pretentious, sanctimonious, over righteous, politically correct euphemisms. If I refer to the facial tissue as Kleenex, or to the pen as a Bic, we all get it. Of course there are other companies with competing products and trademarks, but in wounds (and medicine in general), we use a lot of singular tools and products with no competition, no generic designation, and no pronounceable name other than their well known proprietary ones. I have a name, you have a name, we all identify things by their names. So, if I mention a product by name, let the political correctionists bemoan the fall of civilization and their loss of petty control. I don't care. Nor should you. I will do my part and teach. You will do your part and take it all in and decide if it is meritorious and worth remembering.

(And no, I do not own stock nor proprietary interests in any company I am discussing, but even if I did, you decide . . .)

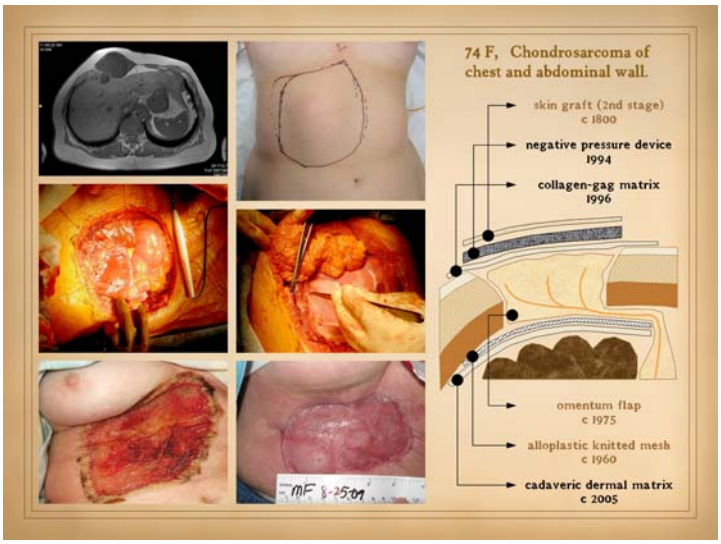
(The image is a watercolor illustration, one of several painted by artist-illustrator N. C. Wyeth to illuminate the novel "Arizona Nights" by Stewart Edward White, 1907.)



3
Integrating New Products and Technologies into Practice #1
New products, why they are important, and why you should care.

Medical arts and sciences evolve, and all practitioners will, in the course of their careers, be expected to understand the advances that support better care of the patient – new medical knowledge and also new products and their usage.

Writing home on an adjustable table. From "Hospital Life in New York", Harper's Monthly v57, July 1878. This article proudly described the advances in architecture and administration that were changing society for the better, reforming invalid hotels into modern hospitals. Amenities of private or limited occupancy rooms, and even the convenience of a bedside table upon which to write or get your meals were obviously significant enough for the authors, illustrators, and publishers of this article to call special attention to them.



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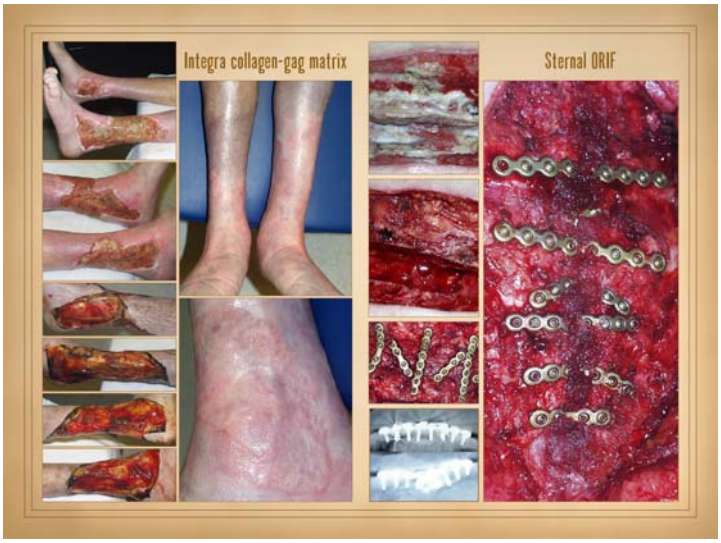
To illustrate the value of worthy new products, let us start with a case presentation. This was a very recent patient, 74 year old woman, with a chondrosarcoma of chest and abdominal wall. Excision of the tumor was legacy surgery – just cut it out – but the reconstruction was based on a combination of new knowledge, new concepts, and new products. The easy efficient uncomplicated good results of this case were achieved doing an operation that was neither possible nor conceivable just 25 years ago when I started my surgical practice.

The open chest and abdomen needed structurally stable repair which would endure for years without the need for later hernia surgery. Alloplastic knitted meshes have been with us for 50 years. Used properly, they make a structurally sound and long durable abdominal wall substitute. However, we have seen over the years that they also have a high incidence of late inflammatory complications, bowel adhesion-obstruction-perforation-fistula. In the interests of increased biocompatibility, biomatrices of cadaveric dermis and fascias have come to market. In this case, a layer of cadaveric dermis was used as the first layer of the reconstruction for its biocompatibility. A conventional alloplastic mesh was then used for structural replacement, because this was a true excised abdominal wall defect, and not just a ventral hernia in which the native muscles and fascias could have been repaired. The artificial mesh needs living tissue coverage, and this was done by the simplest trouble free method there is, using a flap of omentum, transposed on a thin proper-omental pedicle (making sure that the traverse between matrices and native abdominal

wall was properly overlapped and sealed to avoid late herniation). In the past, simple skin grafts would have covered the omentum (still a perfectly legitimate thing to do), but in the interest of avoiding long term scar contractures on this flexor surface, a regenerative collagen-gag matrix was used for dermal regeneration. Rather than using conventional "tie-over" compression dressing to splint all of this, a negative pressure wound device was used for the fixation for the sake of comfort over the next 4 weeks. When the dermal matrix was regenerated, the final skin graft was placed. Note that this reconstruction made no further incisions on the body, required no autogenous flaps (other than the trivial use of omentum), created no additional pain, created no risk of donor site morbidity nor deficits, had no risk of flap failure nor dehiscence, has no risk of future herniation, required almost no hospitalization, and had virtually no risk of failing, all with predictable and dependable good results that will endure for the remainder of the patient's life, all in a short one hour initial case (plus the later skin graft).

Images: **top left**, an mri showing the tumor; **top right**, lines of excision marked around the tumor; **mid left**, open lung, liver, bowel after resection; **mid right**, insetting the matrices; **bottom left**, 3 weeks later, the Integra collagen-gag matrix regenerating and ready for skin grafts; **bottom right**, the healed reconstruction about 4 weeks after skin grafts.

As a resident in plastic surgery, I was taught to do a reconstruction like this with large autogenous flaps carved from elsewhere on the abdominal wall or other nearby structures, or to use fascia lata grafts and large skin flaps. A good secure reconstruction could be counted on, but not necessarily with good long term competence of the abdominal wall, and with a host of acute risks, complications, and potential failures at the primary site and also the donor sites. Pain, long stay hospitalization, and various donor site problems could be anticipated. I have done it all ways: legacy operations the way my professors did it circa 1940-1970, then now-legacy operations that I was taught to do circa 1970-2000, and now this stuff with simple procedures using regenerative materials, circa 2000 and on. This "new way" I have had to learn and develop in the real world of everyday practice as new concepts have evolved and new products have appeared to support and implement those concepts. This reconstruction had six distinct elements: alloplastic mesh, omentum flap, and skin grafts which can be considered traditional surgery in use for 30 years or more; and cadaveric matrix, regenerative dermal substitute, and a negative pressure device, all items of the past 15 years or less. All surgeons must make their own choices about technique, but for me, I cannot see any value in doing this the way I learned about it 30 years ago. Good concepts and knowledge are crucial in all of these advances, but they mean nothing without a company to make the devices and materials that support those concepts.



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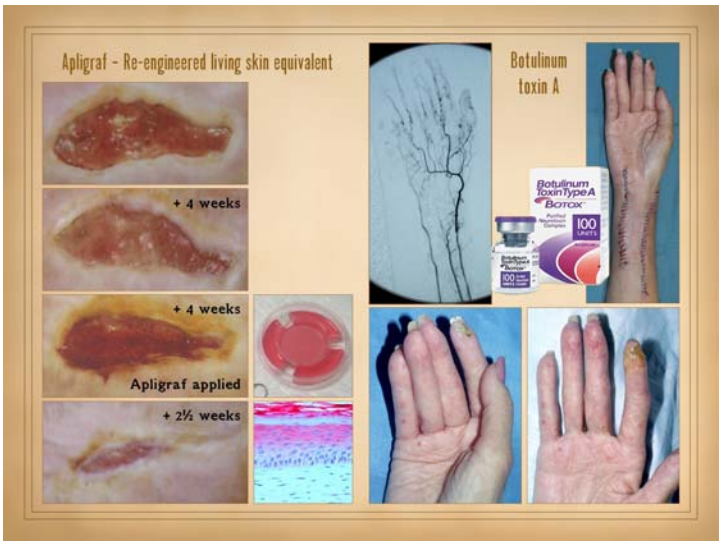
This and the next two slides are a "gallery of the new". These are all patients and problems from my own practice. They represent the things that I take care of week in and week out, and things that I find especially interesting and get my own special attention. That is how progress is made – somebody gets interested enough in a problem to think about it and see a way to get to a solution or a better method. Sometimes you will be the innovator with the novel solution. Many times you will be picking up what some other innovator has discovered, what some other company has made, and figure out how to make it work for yourself, or to extend the utility and scope of it beyond what was originally conceived. The problems illustrated on these three slides have one thing in common – they are all new concepts of the past 15 years or less, things that I did not learn as a resident, things that have supplanted legacy practice because they work so well (easier, safer, fewer complications, more dependable, better results), things that were wholly contingent on the availability of a product made by some company.

Integra collagen-gag matrix: This is an artificial skin and regenerative matrix made from collagen and chondroitin. Originally developed for burn care, it proved to have remarkable properties, and it is one of the most significant advances and products in reconstructive surgery in recent memory. It has a duality of effects. Acutely it is a very high quality artificial skin. When applied to large wounds (burns, fasciitis, degloving), patients rapidly get systemically better. When applied to pathological wounds, inflammation and necrosis immediately cease. Its second role is as the agent of skin regeneration, but unlike ordinary surgery, it arrests normal wound healing and instead triggers an embryonic type of tissue formation without scar. It is a new paradigm in surgery that is not contingent on normal wound healing, and it has found a multitude of uses for acute wound care, chronic wound care, and plastic surgical reconstruction. Illustrated is a patient with a 40 year history of leg ulcers and undiagnosed Sjögren's. Reconstruction and healing of these chronic immunopathic ulcers is impossible with anything that depends on normal wound healing, but is predictable and dependable with Integra, and Integra has become the standard for closing large immunopathic wounds.

Sternal ORIF: Sternal dehiscence after heart surgery was considered a lethal event in the 1960's. By the 1980's, good plastic surgery with conventional large flaps solved the mortality problems, but it was still an issue of prolonged care and morbidity with various acute complications, long hospital stays, and late sequelae. This is a problem in which conventional "dictates", in the truest sense of that word, the "emperor's new clothes syndrome", and a hegemony of misunderstanding of the problem by those in charge of it have turned a simple issue into death and chaos for countless people over the past 55 years. Heart surgeons are not bone surgeons and they are not pus and wound surgeons, so when they get these problems, it always turns into a freakout that treats patients like they are ultra sick until that prophecy is fulfilled. The problem is simply one of sternal mechanics, easy to understand, and easy avoid if you are a bone surgeon, and easy to manage and fix if you are a wound surgeon. Poor sternal fixation with twist wires (the non-bone heart surgeon's traditional and only method of sternal closure) leads to sternal rupture and pseudarthrosis, nothing more, nothing less. If the problem happens, then you do conventional wound care until clean enough for reclosure, and then you close it the way all other bones are fixed, with rigid screw-fixated hardware. The problem can be preempted by plate and screw fixation as well. By using good wound care and plate-and-screw hardware, much of this problem can be managed as an outpatient with little or

no morbidity. The switch from antiquarian no care circa 1960, to what I learned as a resident, legacy sternectomies and big flaps circa 1985, to simplified safe effective bone and wound care of the past 15 years is a fundamental change that was contingent on the products to make it happen, the plates and screws. You can read more about this at the Arimedica website, and also in the journal Wound Repair and Regeneration:

- Resolving sternal wounds by hardware fixation, Gottlieb ME. Wound Repair & Regeneration, 13:A4-A27, March, 2005.
- Online DOI: 10.1111/j.1067-1927.2005.130215a.x
- http://onlinelibrary.wiley.com/doi/10.1111/j.1067-1927.2005.130215a.x



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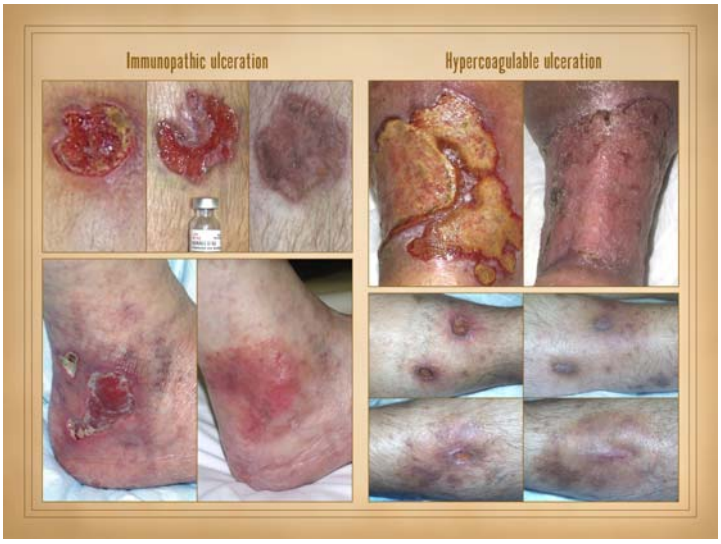
Apligraf: Apligraf is an engineered living skin equivalent. It is normal quintessential skin, dermis and epidermis, grown in culture from donor foreskin fibroblasts and keratinocytes. It represents a class of wound treatments, the living cell therapies, which seem so promising for problem wounds. It is essentially a pharmaceutical packaged in a living vehicle, and the biochemistry created by these juvenile cells has a potent effect to stimulate wound healing. The photos show a plantar wound following trauma in an otherwise seemingly healthy person. The wound had become chronic, and the top image shown was taken many months after the initial events. The two center photos confirm that 8 weeks of simple adjustments to topical care were not effective. Within 3 weeks of placing the Apligraf, the wound is nearly healed (and did heal within the next 2 weeks). There will be more about this product on a later slide, but it is one of those fundamentally different therapies that solves problems and gets results that has come on the scene in the past 10-15 years, and which has forced practitioners to rethink what they think they know and how to do things.

Botulinum toxin A: One of my most favorite operations by far in my career as a surgeon has been the digital sympathectomy and angiolysis. It is done for the problem illustrated, digital ischemia and ulceration due to lupus angiopathy. This is the fibrostenotic occlusive arteriopathy of the hand and foot that results from repetitive acute arteritis, most commonly with lupus and scleroderma-crest. The operation, usually done at the wrist and in the palm, strips away the arterial adventitia to eliminate sympathetic nerve fibers (the digital sympathectomy part), and it can strip away the media in order to correct the fibro-stenosis (the angiolysis part). This operation is essentially 100% effective for patients, and nearly 100% effective for fingers, meaning that all patients have some degree of therapeutic response, and nearly all ulcerated fingers heal. For those who are not yet ulcerated or are in early phases of ulceration and do not need surgery, the same thing can be achieved by chemical sympathetic blockade, using local anesthetic (bupivicaine) blockade of the vessels in wrist and hand. I had many patients who would come in for these blocks, especially during the cold months. Just like the operation itself, these blocks would turn the hand warm and pink, relieving pain and allowing skin lesions to heal. The drug only lasts several hours, but the effects could last a month, and such patients would typically come back every month or so during the winter to get the blocks repeated. Between the blocks and surgery, I thought we had good dependable treatment for this problem. And then, all in an instant, that changed 4 years ago. Some reports appeared that botulinum toxin A had a variety of neuromuscular effects beyond just skeletal muscle blockade, and that sustained peri-arterial sympathetic blockade could be achieved by using the toxin. Favorable results were reported by a couple of groups at the hand meetings in 2005 and 2006. The technique is the same as I have always done with anesthetics, but the effects can last for many months. Instantaneously, my practice changed, and I started using botulinum toxin in lieu of surgery. The results have been amazing. Almost every finger has healed. Every patient gets symptomatic relief for about 4 to 9 months. This is easy to gauge, because our once-a-month patients now get through the winter on one block and come back only after these long intervals. The drug achieves only the sympathectomy effect, not the angiolysis, so for a rare patient, the surgery is still required. However, having consistently done several of these operations every year for the prior 10 years, I have now done only 2 operations in the past 4 years. The clinical results are the same as doing the surgery, and the risks, expense, and overall utility are much better. Regardless of treatment, I like taking care of these problems because it is nice to see scary problems get easy dependable good results. But even when your current practices work very well, when something better comes along, either better results or less risk and expense, then it is time to switch practices. The photos show a woman with scleroderma: an angiogram showing typical disease; the hand after surgery; the fingertip ulcer prior to surgery; and the finger healed a few weeks after surgery. Nowadays, I would just use the botulinum toxin.



7

Sometimes what is new is not a new technique or tool, but rather new concepts and knowledge that guide your overall understanding of disease and treatment. Immunopathic ulceration and hypercoagulable disorders and ulceration are major areas of new knowledge that did not exist when I went through residency, yet they govern the everyday world of chronic and pathological wound practice.

Left upper: Crohn's disease of skin, ulcers healed after intralesional steroids, new lesions prevented from ulcerating by prompt steroid injection. **Left lower:** lupus-rheumatoid-mixed (mctd) with ulceration due to synovitis and panniculitis. **Right upper:** a 43 year old woman, otherwise healthy, but with many years of refractory leg ulcers, and a history of multiple venous thrombosis and pulmonary embolism or thrombosis. The lab confirmed low proteins C&S and low tcpO2's around the wounds. She healed with warfarin therapy and skin reconstruction with a regenerative matrix. She re-ulcerated after she stopped taking warfarin, but then rehealed after resuming anticoagulation. **Right lower:** a 29 year old man with long duration refractory leg ulcers. History and profile were suggestive, and the lab confirmed high anticardiolipins – an antiphospholipid antibody syndrome – and the patient healed just by starting warfarin.

Much more on this subject can be found at the Arimedica website. See especially the companion presentation to this one, given at the same meeting, "(Not) Atypical Ulcers: Autoimmunopathy and Connective Tissue Disorders: The True Intrinsic Diseases of Wound Healing".

8

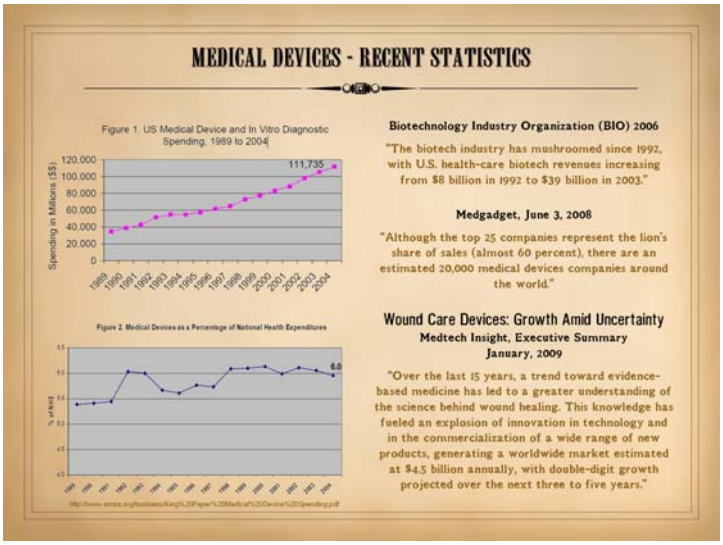
Integrating New Products and Technologies into Practice #2

The ever increasing number of new medical products, and why.

There is an ongoing exponential rise in new medical products and devices. This is attributable to many factors, including:

The general advance of medical knowledge.
Advances in micro-level biological science.
Advances in materials & electronic technologies.
Advances in computer & information technologies.
Career track bioengineering and biotechnology.
Changes in business finance and investment.

A high class microscope from 1876.



9

Here are some recent statistics concerning the health and wealth of the medical device market, including estimates of the wound market. The main message is that the medical device market is big, and getting bigger. Practitioners will face ever increasing new products that will need evaluation and a decision about whether to trial them and use them or not.

Biotechnology Industry Organization (BIO) 2006
"The biotech industry has mushroomed since 1992, with U.S. health-care biotech revenues increasing from $8 billion in 1992 to $39 billion in 2003."

Medgadget, June 3, 2008
"Although the top 25 companies represent the lion's share of sales (almost 60 percent), there are an estimated 20,000 medical devices companies around the world."

Wound Care Devices: Growth Amid Uncertainty
Medtech Insight, Executive Summary, January, 2009
"Over the last 15 years, a trend toward evidence-based medicine has led to a greater understanding of the science behind wound healing. This

knowledge has fueled an explosion of innovation in technology and in the commercialization of a wide range of new products, generating a worldwide market estimated at $4.5 billion annually, with double-digit growth projected over the next three to five years."

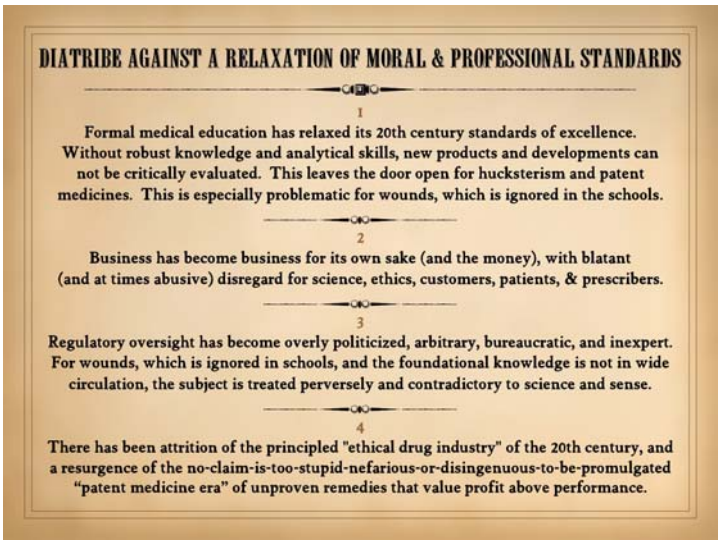
American Medical Student Association
http://www.amsa.org/business/King%20Paper%20Medical%20Device%20Spending.pdf
Figure 1. US Medical Device and In Vitro Diagnostic Spending, 1989 to 2004. [Expenditures tripled over 15 years.]
Figure 2. Medical Devices as a Percentage of National Health Expenditures. [Device spending was a relatively steady percentage of the whole.]

10
Integrating New Products and Technologies into Practice #3
Historical perspectives and the general socio-economic framework of modern medical manufacturing and regulation.

The deluge of new products is good in principle, but the scene is muddled by a relaxation of standards, principles, and ethics, in medical practice, medical education, medical industry, medical finance, business, and government.

Them's fightin' words, but let me make my case, and you just might agree. There's a good chance that many of you agree already anyway without further explanation, but read on . . .

An ad for Lane's Medicine, a laxative and simple tonic, and who could argue with feeling better each morning? It is from The Household, 1892, (a Boston women's monthly). Lane's was a tea, fair enough, but this was an era when, absent any regulation or oversight, vendors could make extraordinary unreasonable claims about meaningless products simply to make a sale. That is the risk today as well.



11
A Diatribe Against a Relaxation of Moral & Professional Standards

1
Formal medical education has relaxed its 20th century standards of excellence. Without robust knowledge and analytical skills, new products and developments can not be critically evaluated. This leaves the door open for hucksterism and patent medicines. This is especially problematic for wounds, which is ignored in the schools.

No, this is not a matter of the good ol' days when, "You know sonny, when I was a kid I had to walk 10 miles in the snow to get to school." Standards have relaxed, No one seems to care. What was once the most literate and educated society on the planet now has some of the most embarrassing performance when it comes to math and science education, letters and arts, history and the humanities. The ultimate spill down is into things like shameful infant mortality and high school graduation rates. For those of us who deal with medical students and residents, there are still some stars, but the average Joe comes nowhere close to the educational and intellectual standards and expectations of a generation or two or three ago. In my own specialty of plastic surgery, the noble arts of putting things back together, and the scientific leadership in wounds and other subjects like peripheral nerves has been subjugated to near oblivion, the flame kept alive by just a few, while the membership at large runs retail cosmetology stores, under the guise of a professional office, and confuses essays on buttock esthetics with real science. Young doctors today seem insufficiently schooled and skilled in math, physics, chemistry, and basic biosciences, not enough that they can make learned and insightful judgments about new products and technologies. And that is not just their fault. It is the fault of the enablers, the people who run the schools who are supposed to be guardians of the curriculum and the morality of education. Post-graduate educational experiences have been corrupted. CME is trivialized to the point that real learning is damned in favor of petty certificates that must be paid for. Restricted resident work hours mean restricted education, learning, maturity, and commitment. In response to a few sensational media circuses about tired residents, the system was re-engineered so that instead of incidental mishaps, now everyone is systematically dumbed down and everybody enjoys a democratically egalitarian dose of mediocrity or worse. American medicine has dumbed down, and it is getting worse under the self-serving guidance of for-profit stakeholders and an amoral disengaged dysfunctional government. And it is all the worse for a subject like wounds which gets insufficient curriculum real estate to begin with. Without well developed minds, charlatans, hucksters, and pitchmen thrive and profit, and the genuine quality of life declines.

2
Business has become business for its own sake (and the money), with blatant (and at times abusive) disregard for science, ethics, customers, patients, & prescribers.

Much of society has been corrupted over the past 20-30 years by an obsessive quest for money for its own sake. It is manifest in the decimation of companies and industries, a deterioration of medical practices, priorities, finances, and moralities, in the corruption of banking and businesses, in the willingness of overpaid and underperforming executives and their boards to bankrupt their companies for their own gain, an evaporation of customer service and concern for users and employees, a disregard for quality and value, an outsourcing of services and skills that has bankrupted our own sustainability and self-reliance, the switch from "the customer is always right" to "whatever our short term day-trading investors want", chaos and deterioration of our system of copyrights and patents, fraud in journalism, fraud in science . . . I could go on, but you already know all of this. There is good news too sometimes, but I defy you to read the newspaper and conclude otherwise. This has extended to the medical industry, where big pharma spends a huge budget on direct-to-consumer pitches and making-of-markets of questionable products, including novel-but-irrelevant compounds and so-what-slice-of-the-pie-me-too products solely for profits sake. In recent years, many time honored basic and categorically necessary drugs, such as autonomic agonists and antagonists, and urinary antiseptics have disappeared because the profits are not there on non-patent properties, while at the same time cosmetic pharma is exploding with drugs to make your penis bigger, your eyelashes longer, and your orgasms warmer and fuzzier. Just weeks ago (September 2009), one of the bulwarks of the traditional "ethical" pharmaceutical industry, Pfizer, was fined $2.3 billion for deceptive and fraudulent advertising and illegal making-of-markets for a number of drugs in its portfolio (that's a big fine). The allegations were not about incidental oversights or grey-area mistakes subject to interpretation . . . this fine was levied against a sustained, systematic, and deliberate perversion of ethics and legality . . . and big companies everywhere seem to think that nowadays this is all okay. Remember what was said on slide 2, "Not all companies are angelic, but companies and products are not intrinsically evil. It is up to users and prescribers to understand what is of value or not." It is just that in this day and age, when moral highroads have been overpaved with overpromises to the land of the greenback, users need to be a bit more wary, a bit more cynical, a bit less trusting, and thus a bit more educated and self-responsible for getting and evaluating information properly.

3

Regulatory oversight has become overly politicized, arbitrary, bureaucratic, and inexpert. For wounds, which is ignored in schools, and the foundational knowledge is not in wide circulation, the subject is treated perversely and contradictory to science and sense.

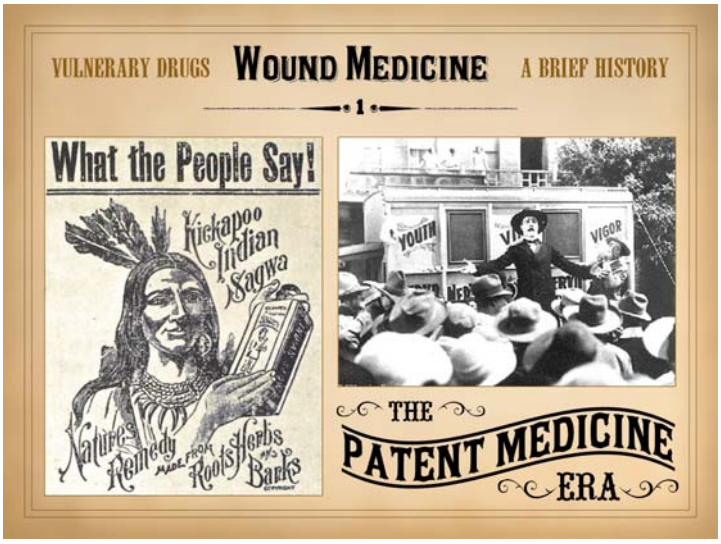
The United States Food and Drug Administration was established by the Pure Food and Drug Act of 1906. That was an example of government at its exemplary best, and it made our food supply and medical industry the best and safest, most advanced and productive in the universe. But that has changed in recent decades. Personally, I see the FDA as still largely righteous and morally oriented, still mostly the good guys, but the FDA has also made the news a lot in recent years for its politicization, inefficiencies, and mistakes. For wounds, the problem is that this subject is already ignored and misunderstood by a medical establishment that is largely 100% uneducated and misinformed about the subject. Wounds are not heart disease, diabetes, cancer, nor anything else that gets big funding and expertise – sad given how important this infrastructure subject is to all of biology. It would be as though the government set up an agency to resuscitate the automotive industry, and in so doing, hubcaps, vanity lights, and upholstery got funded, but metallurgy, electronics, and rivets and welds got ignored, and machinists and engineers were never consulted. For those of us who have observed wound drugs and devices for many years, or have even had some direct participation with that agency, it is clear that there is no wound expertise, and a whole lot of wound naivete. The result (just speaking about wound products now) is that goofy and irrelevant products come to market with no valid science behind them, goofy or bad products come to market with inept and erroneous science behind them, that lame products come to market with unrestricted indications, that good products come to market with inane restrictions on use, good products don't come to market timely or at all, and that companies are permitted to use false, erroneous, inaccurate, and misleading marketing materials to promote products good and bad. Wound protocols, study designs, and endpoints that are expected by the agency are mired in anachronistic irrelevant concepts that might apply to asthma or hypertension drugs, but not to wounds. But what the hell, it's all about the money anyway . . .

4

There has been attrition of the principled "ethical drug industry" of the 20th century, and a resurgence of the no-claim-is-too-stupid-nefarious-or-disingenuous-to-be-promulgated "patent medicine era" of unproven remedies that value profit above performance.

The Pure Food and Drug Act of 1906 and the FDA put the cabash on patent medicines 100 years ago, and that was a good thing. Now, hucksters, pitchmen, and anybody with anything to sell, including once-principled pharmaceutical companies are now looking for ways to make any claim and get any product in front of your face to sell it to you. We hear all kinds of direct-to-consumer advertising for drugs that treat contrived problems that no one ever heard of. Even good but exceedingly dangerous drugs, like clopidogrel (Plavix®) get pitched direct to users. And a lot of it is predicated on FUD, fear-uncertainty-doubt, scaring people into using your product, or cajoling them with retail lifestyle products of no legitimate medical purpose. When big pharma arose and supplanted patent medicine practices 100 years ago, the industry was designated "ethical pharmaceuticals" in which sales and marketing were done only to the physician, not to the patient-user. The companies now want to do end-runs around the profession, right for the money shot at the consumer goal line, something which is easy to do when government ineptitude and behind-doors corruption is blatant, and educational and moral standards among physicians are mired in who-me?, i-don't-know, and who-cares.

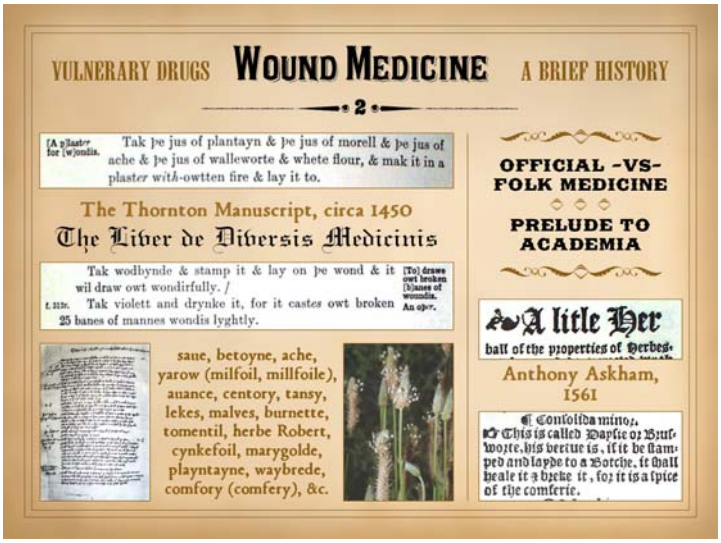
Yes, this is a diatribe. This is my paper. I have the soapbox. You could have stopped reading, but if you are reading this sentence, then you got this far. Agree or disagree, your choice, but unless you are living in a cave somewhere, you know there is truth in here. Why discuss it? Because it affects the products that are coming to market and your chances to discern the truth and discriminate good from bad, wheat from chaff, to "see through" the emperor's new clothes, to not be spammed, scammed, and sold, to maintain some principles and morality, to be someone that your patients can trust to make principled and educated decisions and recommendations on their behalf.



12
Wound Medicine: Vulnerary drugs, a brief history # 1

This presentation is obviously about the commercial medicine trade of today, and in so being it must also reference and allude to the patent medicine practices of the 19th century. This is a good place to make clear the distinction between bogus patent medicines, legitimate pharmacy and therapeutics, and the murky in-between of pseudo-legitimacy that can run roughshod over the unwary and indiscriminating practitioner. This is best understood by a brief precis of medicinal and pharmaceutical practices in history.

When we talk about the "patent medicine era", we are referring to a chapter in the annals of 19th century capitalism. It was a time when an unbridled enthusiasm to make money allowed any devious entrepreneur a chance to play on people's fears and uncertainties about their life and health in order to swindle them of their hard earned money in exchange for a bottle of magic elixir. (Come to think of it, that sounds an awful lot like the practices that are re-emerging today – but perhaps I am too cynical.) This was the era of P.T. Barnum and the quote, correctly or incorrectly attributed to him, that "there is a sucker born every minute". This was the age of the advent of industrial production, the concept of products and branding, and the mindset and ability to make markets out of manufactured goods that could be advertised in nationally distributed publications and sold by mail, rail, and traveling shows in remote markets. Newspapers and magazines of the latter 19th century were filled with ads for miraculous cures, medicines packaged in bottles with fancy labels and pretentious descriptions. People's anxieties (fud) about their health will always be the front door to legitimate medicine and pharmacy, but even more so to disingenuous hucksterism. No surprise then that some of these 19th century cures were legitimate products, but many not. **Right:** for the penultimate salesmen of the era, there was nothing quite so glamorous as the traveling medicine shows. This is a still from an old silent film, circa 1920 (I cannot locate the source) portraying the patent medicine shows as presumably they really happened. **Left:** an ad for the Kickapoo Remedies, a prolific print media and medicine show marketing endeavor to sell patent medicines nominally based on Kickapoo Indian traditional remedies.

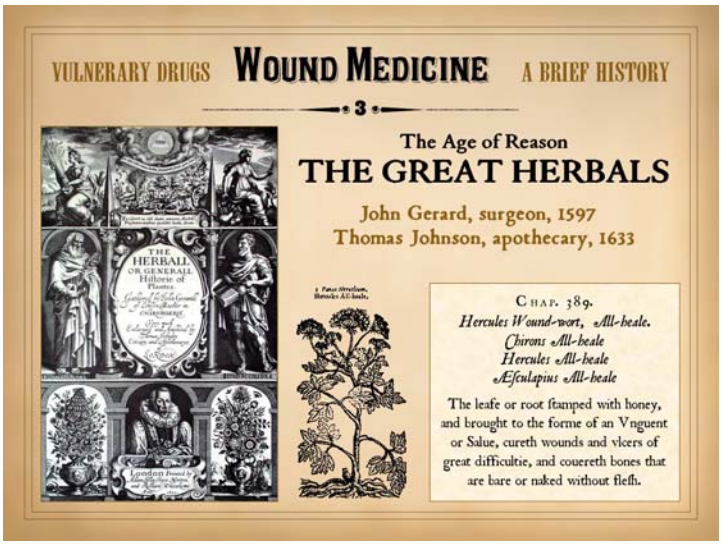


13
Wound Medicine: Vulnerary drugs, a brief history # 2

A crucial distinction must be made between patent and bogus medicines versus traditional and historical materia medica. The modern physician, anyone educated after the mid 20th century, will tend to look down or askance at traditional remedies. Most modern doctors will equate the pejorative "folk" and "herbal" remedies with Granny Clampett and tree-hugging granola crunchers of the hippie commune persuasion. Any such doctor ought not be so self-righteous, because (1) most of our important pharmaceuticals come from plants and other natural sources, and (2) while that doctor may believe he is the arbiter of what he chooses to prescribe, choosing only proper modern medicines, the reality is that many prescriptions are a subliminal hoodwink, a consequence of the manufacturer's false persuasions and fud-marketing bolstered by inadequate physician education. To understand the importance of the natural materia medica, a bit of historical perspective is needed here. Industrial, biological, and pharmaceutical chemistry had their advent in the mid 19th century, leading to the first synthetically manufactured drug, aspirin, marketed in 1897. However, aspirin had its origins in natural plant compounds. In fact many of the most important drugs in use, now or ever, are gifts from nature. The purely designer-made drugs that are the focus of modern patent-and-profit marketing are beasts of just the past 30-40 years. The catalogs of the major pharmaceutical companies of the first half of the 20th century – the Lilly's, Merck's, Abbott's, Upjohn's, etc. – list pages of pills that are distilled, purified, or resynthesized botanicals and biologics. These were the major medicines of most of the 20th century. The standard U.S. medical curriculum up until the mid 1930's included not just the pharmacology that we might think of today, but also botany and pharmacognosy. Why? Because up until recent times, most medicines were derived from natural sources (and many or most still are). Knowledge of these remedies comes from thousands of years of cultural awareness and natural observation and experimentation from communities all around the world. What modern doctors might disparagingly think of as "herbal remedies" were the legitimate remedies – the only remedies – of organized, academic, sanctioned, "official" medicine right up into the 20th century. Prior to 1850, there was no knowledge about the chemical structure of organic molecules, no ability to do pharmacokinetic studies, no awareness of what a receptor molecule was, not even the definition of the "therapeutic index". Yet the knowledge of pharmacological effects and therapeutic properties was deeply understood for many thousands of plants and other natural materials. Well documented pharmacopeias and compendia of natural remedies have existed in Europe and China for well over two thousand years, and cultures across the globe had their own materia medica of great diversity. And just like with spoken languages and other oral traditions worldwide, cultural heritage and knowledge of these subjects is disappearing more quickly than it can be recorded.

Left: The 14th, 15th, and 16th centuries in Europe saw the advent of the herbals. These were compendia of medicinal knowledge and the properties and uses of plants and their remedies. Medicinal compendia go well back in Western history, including works such as the Smith and Ebers papyri from Egypt, Anglo-Saxon leechbooks, and the works of Hippocrates and Dioscorides in ancient Greece. But in Renaissance and post-Renaissance Europe, the resurgence of knowledge and academia led to beautifully detailed (and in latter centuries, beautifully illustrated) books trying to organize all of this knowledge. Illustrated are pages from the Thornton Manuscript in England, circa 1450, entitled The Book of Various Medicines. The remedies illustrated are for wounds. The first recipe is "Take the juice of plantain and the juice of morel and the juice of ache and the juice of wallwort and wheat flour, and make it in a plaster without fire and lay it to." Plantain (plantago spp., pictured) are one of the most oft-repeated and pre-eminent vulnerary (wound healing) herbs throughout the greater European materia medica. So too are many of the others quoted in this book, such as comfrey (Symphytum, "knitbone") and yarrow (Achillea, "Achilles woundwort"). Because wounds do not get interest and funding like heart and lung disease and cancer, these remedies and their unique chemical compounds have gotten extraordinarily little attention on the front lines of crude drug research, so their potential properties have never been explored. One of the few that has been studied is comfrey (Symphytum officinalis), and it is full of allantoin, which is available as a modern medicinal product for wounds.

Right: Speaking of comfrey, here is an excerpt from Anthony Askham's "A little Herbal of the properties of herbes", 1561 in England. The entry is for "Consolida minor. This is called Daisy or Bruisewort, his virtue is, if it be stamped and laid to a Botche, it shall heal it & break it, for it is a spice of the comfrey." A modern doctor who has not studied medical history might dismiss all of this as "herbal medicine", but these herbals were the legitimate, official, sanctioned medicine of the day. They were masterpieces of observational knowledge, and they were the prelude to the great system of European medical academia that was already beginning in this era and would come to full bloom in the latter 18th century. Today, they could and should be a guide to crude drug research for anyone looking for novel compounds that might have a positive effect on wound healing.



14
Wound Medicine: Vulnerary drugs, a brief history # 3

The mid 16th through the 17th century was the epitome of the Renaissance, an era of important observational science that paved the way to the Enlightenment and our principles of scientific thought, investigation, and education. This was the era of the Great Herbals, not just the little herbals of the 15th century, but grand encyclopedic works meant for the professions. Some of these botanical encyclopedias were written by "naturalists", but most were written by physicians, because these were the pharmacopoeias and pharmacy textbooks of their day. One of the greatest of these was the Gerard-Johnson Herbal. The first edition appeared in 1597, during the reign of Elizabeth I, written by Dr. John Gerard, preeminent surgeon and botanist, and herbarist and superintendent of gardens to colleges and crown. Gerard's own first edition copied much from other primary sources, and it had many errors of his own, making it neither correct nor erudite, but it became very popular. In 1633 Thomas Johnson, an apothecary and botanist, was commissioned to undertake a massive revision of the book, including thorough updates and corrections, more accurate illustrations, and many new entries. Scholarly and highly regarded, the 1633 Gerard-Johnson edition, The Herball or Generall Historie of Plantes, became for generations, well into the 19th century, the premiere English source of botanical and medicinal information. (If you love botany, medical history, or old books, the Gerard-Johnson 1633 herbal is available in a huge facsimile reprint from Dover publishers.)

Illustrated is the title page from the 1633 Gerard-Johnson herbal. The plant is one of the entries in that book, Chapter 389. The engraving is, titled "Panax Heracleum, Hercules All-heale." The text quotes "Hercules Wound-wort, All-heale, Chirons All-heale, Hercules All-heale, Æsculapius All-heale. The leafe or root stamped with honey, and brought to the forme of an Unguent or Salve, cureth wounds and ulcers of great difficultie, and covereth bones that are bare or naked without flesh." In recent centuries, these common names are applied to the herb Prunella, not Panax species, and nowadays Panax refers to ginsengs. The engraving illustrates a plant from the Umbelliferae family, and probably refers to Opoponax chironium, a plant from the Near East, from the roots of which is obtained a medicinal (including vulnerary) resin called opoponax or sweet myrrh. One of the problems in reading works more than 200 years old is that common vernacular names, classic Latin names, and modern Linnaean names often do not coincide, making clear identification of species sometimes difficult. As for Prunella vulgaris, this is a common field plant of the Labiatae. It is by far one of the most respected and important vulnerary herbs across all cultures and materia medica. Its common names include all-heal, self heal, Hercules woundwort, carpenter's woundwort, carpenter's weed or herb, and hock-heal.

The fact that a surgeon was the botanist and herbarist might seem peculiar from our modern vantage point, but it was normal and expected in this era. Here is the title of another contemporaneous work, published in Paris in 1583 by Esaie le Lièvre Chirurgien (a nom de plume?), under the extended title (Englished) "Pharmacopoeia and Garden of Military Surgery, containing the instruments and plants most necessary for all Surgeons . . ." Consider another famous contemporary work, the "Booke of Observations by William Clowes, one of her majesties Chirurgions, London, 1596", one of the most important books of surgery from that era, and the first text to describe treatment for gunshot injuries. Gunshot treatments included elaborate pharmaceutical recipes using the important vulnerary herbs, such as plantaginis (plantago, plantain) and prunella. The great French wound surgeon, Ambroise Paré, a contemporary of Clowes and Gerard, made his greatest observations of wound care based on herbal vulnerary remedies. Gerard, in his herbal, described sweet clover, Melilotus officinalis, for its anti-inflammatory and wound healing properties, "With the juice hereof . . . is made a most soueraigne healing and drawing emplaster . . . made by a skilfull Surgion." (Melilotus officinalis has a modern role as well, as it is the source of coumarin.) Wound care, surgery, and herbarism have an important historical and

scientifically validated connection.

The connection between wounds and pharmaceuticals dropped from collective knowledge and conscience at the end of the 19th century. The concept of the pharmaceutical management of wounds simply evaporated as the pathogenic role of bacteria in infections was learned. Wounds are wounds and infections are infections, and the intersection of those two vast domains of knowledge is limited. However, following the contributions of Pasteur, Koch, and Lister, the two got inseparably confused. We are now left with a legacy that most physicians have little or no knowledge whatsoever of wounds, soft tissues, and surgery (and alas many surgeons likewise have marginal knowledge of wound science and therapeutics). For most doctors, a wound is simply an excuse to vent some atavistic aggression under the guise of a blind obsessive quest to kill germs, rather than a chance to study the true arts and sciences of wounds, wound pathologies, and wound therapeutics. And this lapse is not just a sad but honest misdirection of medical knowledge and curriculum. Make no mistake about it, manufacturers and advertisers have exploited germophobia to the maximum to get you and your patients to insist on germ killing products in both the medical and consumer markets. Over the past century, whenever the economy has gotten rough and society is looking for scapegoats, the germ-fascists have consistently pulled the fud-trigger to "persuade" you to buy more antiseptics, antibiotics, and sterility products, and that strategy is a consistent winner. For the past 140 years we have blinded ourselves to the concept of pharmacological control of wound biology, and we have ignored the potential tools found in nature. This has been easy enough to do when the whole subject of wounds has been ignored in the medical curriculum and the average doctor has zero legitimate knowledge of the subject. It is one of the great ironies of wound and pharmaceutical science and practice that, just at the moment in history when we got the knowledge and tools to understand and manipulate biological chemistry and create potent pharmaceuticals, that the knowledge of germs occurred concurrently and aborted any interest in the biological and pharmaceutical chemistry of wounds (and for entirely incorrect, erroneous, specious, illogical, and fallacious reasons). Too bad, because the wound is a biological-biochemical system, and opportunities for the pharmacological control of wounds might be just as rich as they are for cardiovascular and endocrine and pulmonary therapeutics. Over the past 20 years, modern bioscientists have started to redevelop the concept of wound pharmaceuticals. These new or renewed concepts are based on modern high technologies of genomics, proteomics, and other sub-cellular biochemistry. Sadly though, we still have a blind scotoma to the classic aromatic, alkaloid and other organic phyto-chemicals and pharmaceuticals that might help us heal our wounds – the wound equivalents of morphine, digitalis, penicillin, atropine, salicin, curare, quinine, quinidine, reserpine, ephedrine, and other natural chemicals that just might have genuine vulnerary properties. The collective knowledge of vulnerary drugs and potential pharmacological control of wounds is archived in the pre-20th century herbals. It awaits those with modern knowledge and investigative methods to study these biochemical resources and rich repositories of potential therapies. It awaits those whose minds have broken the shackles of blind germophobia and the intellectual anchor of a retarded medical curriculum, mired in the now anachronistic discoveries of 140 years ago, that thoroughly ignores the physiology and pathology of one of the body's most basic infrastructure systems, wound healing.

Reconsider the quote above, "The leafe or root stamped with honey, and brought to the forme of an Unguent or Salve, cureth wounds and ulcers of great difficultie, and covereth bones that are bare or naked without flesh." Comments like this have to be taken seriously, but they also raise an issue that is as relevant today as ever, in fact more so: how do you discriminate a positive therapeutic effect from a passive effect to remove injury and inhibition. In an era when wound care was most likely mostly awful, the use of almost any emollient or non-irritating botanical was likely to have an effect to control pain, inflammation, and putrefaction in a wound. Today, we would just use the terminology "basic wound care" or "wound hygiene". This was the great revelation of Paré, that if you treat living flesh like it was alive, it stays alive and does well. If you kill it with "treatment", it acts dead with all of the adverse effects that that incurs. Paré was a military surgeon who was schooled in the medical and surgical culture of his day, a long lineage from Galen 1400 years prior. Caught in a situation where he had not enough boiling oil to cauterize wounds, he treated them with emollients – egg yolk, rose oil, and turpentine. The improvements in pain and healing were dramatic, and it revolutionized the practices of surgery ever since. So, do rose oil and turpentine have pro-proliferative effects to accelerate wound healing, or is it just that by treating tissues kindly, they live and do what they should? Paré and his contemporaries understood that this was just a matter of good hygiene and being kind and gentle to living things. The traditional materiae medica have many vulnerary drugs that purportedly accelerate healing, and there is a time and place for them, but all wounds deserve to get off to a good start with simple basic hygienic care. That principle has not changed in 400 years, nor will it ever: phase one of all wound care is to get the wound under control, healthy, and capable of healing; then phase two are the discretionary treatments to accelerate healing or promote closure.

The remarkable claims of magical healing attributed to magic potions are a perversion of the 19th century, culminating in the patent medicine practices just prior to the 20th century. Yet the problem is still with us. As will be demonstrated on later slides, many products come to market with utterly ridiculous claims of effectiveness when in fact all that was done was to provide basic wound care. If you provide no care or bad care (which is what many doctors do), wounds will do poorly. If you provide basic hygiene, using whatever safe agents appeal to you or your patient, then wounds behave naturally. Allowing an unimpeded unfettered uninjured wound to do its natural thing without interference by bad care will result in normal natural wound healing at natural kinetics or rates. If the only thing you have ever witnessed is bad wound healing due to bad care, then seeing normal wound healing due to basic good care can easily be misinterpreted as accelerated healing. Sadly, many wound products that come to market are guilty of this misconduct and misinterpretation. Sadly, many wound products coming to market are being developed and promoted by people with virtually no knowledge of wounds, with virtually no clinical experience, who have never seen normal wound healing with basic proper care. Sadly, it is all too easy to dupe the potential buyer because it is easy to baffle people with pseudo-scientific nonsense that purports to show positive results, regardless of how lame or bogus the product and its so-called "clinical research" are. Sadly, the regulatory agencies have such little knowledge of wounds that the bogus studies get through, opening the door to marketing campaigns that might be in good faith, but nonetheless show nothing but the effects of basic good care.

And a final note on the pharmacy and botanical practices of this general era: William Withering. Working in the latter 18th century, 200 years beyond Gerard, Paré, and Clowes, he observed the folk practice of using the foxgloves, Digitalis purpurea, to cure cardiac dropsy, aka congestive heart failure. His well earned fame does not come because he simply stumbled on this practice, as though he was a geographer or explorer or anthropologist on an expedition to some dark jungle or steamy tropical locale. He was a physician and botanist of great schooling and learning and experience, and the foxgloves were a common remedy in his own homeland. He earned his fame because he took this taken-for-granted traditional remedy, saw it through the filter of contemporaneous scientific medical knowledge in the Age of Reason, developed an hypothesis

about its use (this era saw the dawn of the "scientific method"), and then tested these concepts then analyzed the data. Over the course of a decade, he meticulously studied nearly 200 patients, allowing him to report on the proper usage and dosing of this drug in the service of well-reasoned safe and effective medicine. He is the Father of the Clinical Trial. He applied reason, ration, refinement, and standardization to the crude drugs in common use for thousands of years. It is seminal events such as this and the development of aspirin which chart the development of modern pharmacology from its roots in the traditional materia medica of prior ages, and which differentiate genuine good pharmaceutical products and practice from the bogus charlatanism and hucksterism of the 19th century, much of which is still with us or rapidly returning.

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Wound Medicine: Vulnerary drugs, a brief history # 4

As explained above (slide 12), the 19th century saw numerous changes in transportation, communication, industrial production, branding and corporatization, and social systems and sensibilities that opened the door to all things money and melodramatic. From Barnum's Circus to Buffalo Bill Cody's Wild West Show to the Kickapoo Medicine Shows, it was all a romantic and stirring blend of the real and the phony, the legitimate and the contrived. At Buffalo Bill's show, you at least got to see the real Sitting Bull, and got to watch the real Annie Oakley really shoot. You got your money's worth in entertainment. But the purveyor's of magic potions sold you little more than a promise of good health, which you bought, and bought into, because (1) a fool and his money are soon parted, (2) there is a sucker born every minute, and (3) fud sells (fear-uncertainty-doubt). There were of course some real remedies, but the consumer had no way of knowing what was real and what was not. There were no manufacturing standards, no truth in labeling laws, and no guarantee whatsoever that there was anything more than a bit of alcohol and bitters in the bottle. The greatest value of the patent medicine era are the wonderfully whimsical trade cards and labels, and if you love folk art and ephemera, these are one of the funnest things you can collect. Shown are a sampling of some of these cards.

Opodeldoc was a generic type of herbal elixir. Gordak's Highly approved Opodeldoc was an inestimable remedy for the Rheumatism, and also a long list of other things, including ". . . it speedily cures violent Bruises . . . and is also a most excellent Salve for Sores, and is well known to heal the hardest wound in forty-eight hours." Alas, if only I could prescribe such a miracle for my own patients, but forsooth I dream too much. Dr. Thomas' Eclectric Oil, made with electricity, was "capital for burns, bruises, cuts & sprains," and just about anything else what ailed you. Other manufacturers also made "eclectric" [sic] oils, and all manner of bizarre concoctions, therapeutic claims, and advertising gimmicks are to be found on similar trade cards. Notice one of the gimmicks that is at work here: pseudo-legitimate faddism and buzzword marketing. This card appeared at the dawn of practical electricity, when the telephone had been established, electric lighting was coming on line, and electric motors were starting to revolutionize industry. Electricity was still a new, novel, and mysterious thing. (Even though the nature of electricity was still mysterious, its association with biology had been made by the early 1800's. This only served to heighten its mystique, so much so that Mary Shelley, who was quite aware of the works of Galvani and Volta, wrote a novel about the subject, one of the earliest works of the science fiction genre. "Frankenstein, or the Modern Prometheus" is a dark gothic insightful look at the moral dilemmas that might ensue from the then plausibly hypothetical scientific possibility that electricity might reanimate biological systems.) Not surprisingly, the mystery, power, and potential usefulness of electricity were quickly exploited by those wanting to sell you something for your health. All manner of electrical and magnetic medical gizmos appeared for all kinds of ridiculous reasons. And just because you can't put lightening in a bottle didn't deter the proprietors from saying just that, that there was "eclectricity" in that joy juice. That it was all phony just didn't matter, because it was all new, mysterious, romantic, and beguiling, the stuff that every sucker with a dollar to yield was going to buy, simply because it sounded modern and scientific, and you literally couldn't live without it, or so the fud-mongers sold you.

Contrast these patent medicines with the lost waifs of pharmacy, the traditional materia medica with long histories of vulnerary usage, but which have not been addressed by modern scientific and clinical methods nor funding for crude drug research. Pictured is the common mullein, Verbascum thapsus, naturalized from Europe, and found throughout the temperate United States (the photo here was snapped along Arizona's Mogollon Rim). Before the 20th century, when pharmacists compounded the doctor's prescription, mullein was a common ingredient for soft tissue problems. It has a long history of medicinal use, suitable for wounds, swellings, inflammation, and the like, and possibly the best remedy ever for the piles.

16
Wound Medicine: Vulnerary drugs, a brief history # 5

At the turn of the 20th century, the patent medicine trade gave us some gems such as the one illustrated for Henry's Carbolic Salve. In words which Keats, Shelley, and Byron might have envied, we read an idyl of the poetic and passionate romance between Alphonso and Imogene:

> Alphonso loved dearly the blithe Imogene
> whose face was the fairest that ever was seen,
> but when he proposed, "alas", Imogene said "
> I would gladly accept and with thee would wed
> but with ugly eruptions your face is so scarred
> that all my life's future, with you would be marred
> unless you remove them, so if me you'd have
> you must cure them with Henry's Carbolic Salve.

Notice Alphonso's sad countenance, tortured by the ravages of a great pestilence, and the disgruntled demeanor of deprecation and detestation on that demoness's face. Had Alphonso any good sense, he would have moved on to brighter prospects, but happily or sadly this tempestuous affair was saved by the greatest invention since warpaint, Henry's Carbolic Salve. In a miracle of industrial era marketing, the trade card was a foldout. When you opened the lower flap, chapter two of the story literally unfolded before you, a happy and sanguine turn of events that should make you weep for joy, as undoubtedly it did for our lovebirds, as can be seen on their coy smiles:

> Alphonso this remedy tries – and again
> pops the question – nor does so in vain
> Henry's Carbolic Salve has swept his face clean
> of every unsightly spot that was seen
> As a compound for healing it's speedy and sure
> and for burns, cuts, and bruises, readiest cure.

Thankfully for poor Alphonso he lived at a time when Imogene knew not of the penis enlargement products that grace the advertising media in our own enlightened era. The back of that trade card got down to the gritty technical details about Henry's Carbolic Salve, including, "The most powerful healing agent ever discovered . . . heals burns, cures sores, allays pain, cures eruptions, heals pimples, heals bruises. Ask for Henry's and take no other. Beware of counterfeits." And here is what you need to understand . . . This was not quaint and cutesy when it was published 120 years ago. Sure, it was a bit folksy, meant for a lay rather than a professional audience, but nonetheless it was au courant, up-to-date in the printing technologies and artistic styles of the day, hawking a product that was on the forefront of legitimate practices and progress of that era. No one then would have laughed at this ad as a quaint antique. Much of what abounds in medicinal marketing today is just as fake, phony, and bogus, and will be seen as just as ridiculous and retarded by our descendents in 2130, assuming that society and culture have not totally imploded.

Henry's Carbolic Salve "was on the forefront of legitimate practices and progress of that era." In understanding how to assess new products and technologies, you need to understand the pernicious and insidious effects of pseudo-science and pseudo-legitimacy in marketing, and this is a perfect example. The germ theory of disease and the principles of antisepsis for wounds and surgery were established by Pasteur, Lister, and Koch. Joseph Lister was the one who brought these concepts from the lab and veterinary practice into the clinics, and he published his first treatise on the subject in 1867. He used carbolic acid, aka phenol, as the means to disinfect the surgical environment – killing germs on instruments, supplies, furniture, etc. (as well as using gloves and gowns and other means of avoiding germ exposure). His contributions revolutionized safe surgery as much as the advent of anesthesia in 1847. By about 1890 these concepts had prevailed, and antisepsis became routine practice in hospitals and surgery. Carbolic also found its way into consumer products, such as carbolic soap. Phenol is actually quite toxic, so it has been supplanted by other antiseptics, but the historical role of this chemical cannot be overstated. However, it is easy to see how the use of carbolic, or any antiseptic could have then been taken to the next step, beyond its well-reasoned use in surgery, and extrapolated to any problem rightly or wrongly assumed to be associated with germ-induced disease.

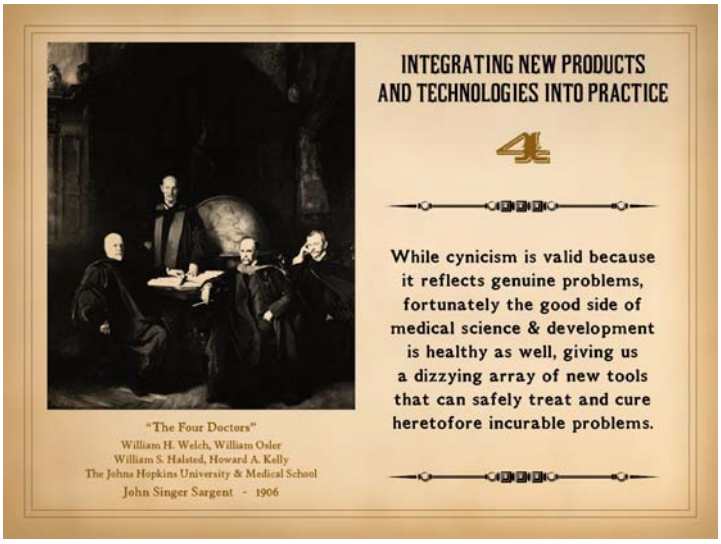
When a product such as Henry's Carbolic Salve appeared, in was a good-faith product. It fit with contemporary knowledge. It made sense at the time that if carbolic could disinfect things, then just kill the germs and all disease would go away. That concept is of course incredibly naive and uninformed, but it was in part the best knowledge of the day, and it was certainly the fad of the day (and for the past 120 years). Controlling exposure to germs and avoiding contamination and inoculation are important (the reasons for using carbolic), but the unspoken assumption after all of this was that all disease and adverse medical events could be attributed to a germ . . . just kill all the germs, and human disease will go away. Killing germs thus became the crusade, and soon enough it was a self-indulgent crusade for its own sake based on germicidal germophobia and a catechism of sterility. In the case of poor Alphonso, this blind zeal completely ignores the true pathogenesis of the acnes, and it eschews all relevant therapy other than killing germs, but the problem was rooted not in Henry's product, but in the assumption that germs were really the issue. And like any great new body of knowledge that comes to light, as germs and infectious disease did in the latter 19th century, it is easy for everybody to have an overzealous vision of the problem as seen through the discolored spectacles of that latest discovery. If the same zeal and money went into quality physician and allied professional education on this subject as goes into the marketing of germ killing products and germ killing quests at hospitals, then actually morbidity would be dramatically reduced. (Of course, the problem was made all the worse when we got internal germ killers – antibiotics.) All of these products have a vital role in treating genuine infections. But a huge part of the profit-making sales and use of these products is for non-infections. When proper germs are in proper places, they are benign, and oftentimes they serve our own

vital health within the complex ecosystems of our bodies. Nonetheless, all one has to do is demonstrate that there is a germ in the neighborhood, and doctors have a Pavlovian response to whip out their antimicrobial artillery. The use of these products is based only partly on science and legitimate practice, but much more on fallacy, fad, and fud, born out of inadequate and inept medical education on this subject, and stoked and cultivated by medicinal manufactures who make large profits through prescribers' ignorance, gullibility, and primal fears of these subjects. All of this is a consequence of a 20th century society that rewards fud-based marketing more than it values proper medical education and rational doctoring.

As we have already stated, wounds are wounds and infections are infections, and the two domains have only a limited intersection. But combine a lack of good education about physiology and pathology with a healthy dose of marketing capital and cleverness, and it is easy to sell you products like Henry's Carbolic Salve. It was a pseudo-legitimate product. It had some basis in contemporaneous science. It was conceived of, manufactured, and sold in good faith, with the naive but fair belief that it could do the things it espoused. Of course, that product was never going to clean up acne scars, and no pitchman with a breath left in his body was going to pass up a chance to overstate and overplay the product to boost sales, and caveat emptor the buyer had to beware, but nonetheless it had some perceived basis in reality. And that is the problem with many products, both then and nowadays. If your knowledge of a disease or clinical problem is marginal, and some manufacturer with equally little knowledge is trying to sell you something that fits the fad and fud of the day, then you can be sold. Yes, there are products like that, where a company of technologists has the capacity to make a product and the capital to bring it to market, but none of the knowledge or expertise of the specialists who will buy it, prescribe it, use it. In the 1880's, it was electromagnetic gizmos made by electrical men who knew nothing about pathology and clinical medicine. In our own times, it is bioengineers who manufacture altered genes and proteins, because they can, to make products that clinicians never asked for, but will buy for no reason but that it is new. Many such products are sold in good faith, with buyer and seller, manufacturer and professional prescriber all on the bandwagon, all bowing to the emperor's new clothes, all naively thinking that the product is good. Such products are moral, even if pointless, erroneous, misleading, and dangerous. Sadly though there are also the immoral products from deceptive manufacturers and pitchmen who know that there is no point or value to the product, or who lie and mislead and tamper with the data about safety and efficacy, with no moral other than to make money. In the 19th century, there was a lot more deliberate ripoff and deception. The need to stop that prompted action by the federal government via the Pure Food and Drug act of 1906. Since then bad products have been more of the good faith naive kind, but in the past 10 years we have seen a resurgence of the immoral kind. It is up to the prescriber to be sufficiently educated and sales-resistant in order to properly evaluate new products, selecting items based on genuine needs and robust knowledge, rather than falling for glamorous pitches that appeal to your shopping impulsiveness.

To summarize, in the latter 19th century we learned that germs cause disease. They cause some of what had been the most fearsome, lethal, refractory diseases of the day – syphilis, plague, tuberculosis, diphtheria, pertussis, measles, smallpox, anthrax, and on and on. That knowledge was not just an epiphany, but a signpost pointing the way to look for cures for those diseases. Lister was one of the first to find a weapon against the microbes, in the form of carbolic antisepsis. In the enthusiasm and revelation of this new knowledge, everyone's attention got focused on germs as the arbiter of not just infectious diseases, but of any and all disease, and anything that could kill a germ became a selling point for the whole spectrum between legitimate research and ersatz patent medicines. Henry's Carbolic Salve was a pseudo-legitimate product, swept in on this tsunami of contemporaneous medical knowledge because it fit the romance of killing germs to cure human illness. But the false pretenses and true predicates behind Alphonso's problem were ignored, overlooked, or misunderstood. Henry's Carbolic Salve might actually have been beneficial for Alphonso, serving as a "chemical peel" that would have helped the scars and epidermal dysplasia, thereby bolstering the erroneous belief that killing germs was the relevant virtue (see slide 34 for more about this). We do the same thing in our own modern times – it is just human nature to try to explain the unexplained with the latest revelation. In just the past 20 years, wound practice has seen the same mentality toward collagen, growth factors, and MMP's (matrix metalloproteases). As we elucidated the role of these chemicals in the process of wound healing, there arose the belief that any of these would be the salvation of all wound problems, and many companies geared up to produce products based on the chemicals, and to make marketing campaigns built around the buzzwords. Alas, the wound is a complex system with diverse pathologies, many of which cannot be affected by these magic bullets, and the skew between comprehensive reality and the product-of-the moment is vast – but blessings to those who look for answers, because eventually we do find things that work.

At the turn of the 20th century, there arose in Europe and the United States a legitimate and productive ethical drug industry. This was concurrent with the rise of a high quality system of medical education and an explosion of medical technologies and science. The first half of the century laid the foundations of a true scientific approach to pharmacy and drug development. In the latter half, after World War II, the ascendency of precision manufacturing and of electrical and computational technologies saw the advent of biomedical engineering and devices. The patent medicine trade of the 19th century was relegated to oblivion by the 1930's. Most of the 20th century was a period of pride, admiration, and respect in medicine and pharmacy. Whether that righteousness was more real or perceived, this was an era when morality, civility, and government and quality regulation were expected and respected. So too, the companies and their products were accorded esteem because they seemed to stay within the bounds of morality and legality and fairness and respect for customers, patients, and providers. In recent years though, the genuine idealism and morality of our historical icons – Washington, Lincoln, Hamilton, Franklin – have faded to mere shadows of themselves engraved in green ink. And speaking of Washington, while oversight and regulation have gotten more picayune and stupid in many ways, they have also weakened and become inept in some ways, permitting a "when the cat's away, the mice will play" opportunity for the companies and vendors who stake a claim in the giant shopping mall and flea market of medical products and manufacturing. It is reassuring that the government can still catch and sanction a once principled "ethical" pharmaceutical company like Pfizer, but it is a shame that such violations could have or would have happened in the first place. But they are – that's the reality of today. The front line of defense against all that is not righteous and just is YOU. YOU are the bastion of quality and respectability that your patients expect and deserve. There are plenty of new products out there, some great, many good, some so-so, some no-no. How do you know which is which? It is up to you to discover. How? By being educated about wounds and new products, responsible and disciplined in your evaluation of them, and having the composure to reject the bad, embrace the good, and be neither intimidated nor beguiled by the products nor their companies nor their pitches.



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Integrating New Products and Technologies into Practice #4

The importance of medical products to advancements in practice.

You might think that I am being strictly cynical and jaundiced. No. Now that that is out of the way, here is the flip side. While cynicism is valid because it reflects genuine problems, fortunately the good side of medical science & development is healthy as well, giving us a dizzying array of new tools that can safely treat and cure heretofore incurable problems.

This is the famous painting by John Singer Sargent, 1906, of "The Four Doctors" at the Johns Hopkins University & Medical School: William H. Welch, William Osler, William S. Halsted, Howard A. Kelly. These men, working at the turn of the 20th century, had much to do with the organization and curriculum of modern medical schools and the post-graduate residency system of medical education. They iconify the advent of American medical education and science and the great scientific progress and clinical triumphs of the 20th century.

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This slide lists just a few of the changes in medicine in recent years that might be considered revolutionary, fundamentally changing the way we approach problems, changing the safety and efficacy of what we do for the betterment of our patients. Some of these changes are hardware and device based, such as orthopedic implants. Some of these are devices in the new class of biologics and regenerative medicine and surgery, and some are cutting edge biologic therapies based on genomics and proteomics. Some represent procedural changes supported by complex technologies, such as endo-surgery. Some represent logistical improvements, such as the ability to respond rapidly to coronary and cerebral thrombosis. Some are diagnostic tools such as pet and mri, and more importantly, some are the ability to distribute the results quickly, such as information and network technologies. Some are the integration of the body with electronic technologies. Some, such as gene chips and gene therapies, are at the forefront of micro-scale science being useful for clinical practice. And surprisingly, something such as the conquest of peptic ulceration results from the same observational medicine that made great strides in the 18th and 19th centuries, but seen through fresh eyes, open minds, and a renewed sense of interest in basic pathology. All of these advances depended 50% on new knowledge, forward thinkers, ardent advocates, and dedicated scientists, engineers, and clinicians. The other 50% were the devices and technical developments that allowed new and good ideas to come to tangible realization and functional fruition via for-sale manufactured products. Without product concepts and companies to engineer and manufacture them, these advances would have remained the perpetual dreamscape of some far-in-the-future fantasy world, while we ourselves would have remained huddled in the cold in our pre-paleolithic caves.

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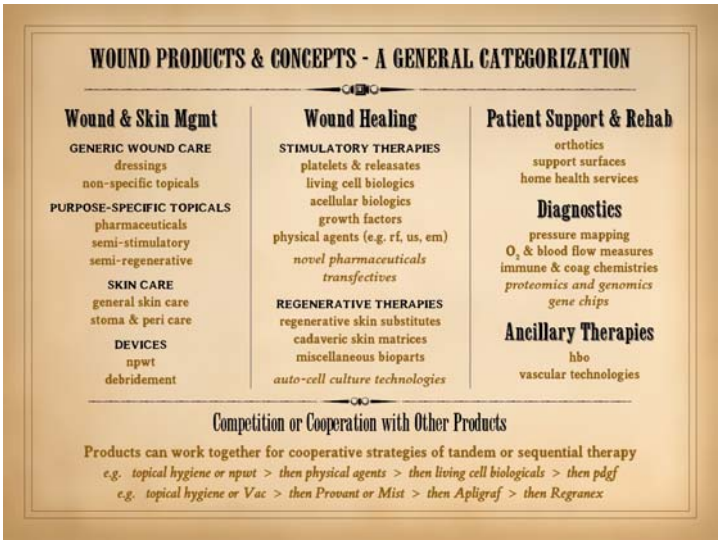
Integrating New Products and Technologies into Practice #5

Guidelines for assessing new products: general product categories.

We have established that the practitioner will be barraged with new products, good and bad, bogus and legitimate. The purpose of this presentation is to try to give some guidelines for these questions: How do you evaluate new products, to decide which ones are theoretically meritorious or not? If you find yourself on the front lines of working with new products, how do you decide which ones you are going to try for yourself, and how do you conclude if they have a worthwhile role in practice? How will you recognize good from bad products, good from bad companies, good from bad effects and results? If a product is proving itself, how will you integrate it into your own daily practice, and also how will you help others to understand how to use it? As shown on the next slide, this starts by sorting out products by type and purpose.

An advertising cut for Quina-Laroche, appearing in Scribner's Magazine, 1890. This remedy is legitimate. Malaria is a scourge that we still have

yet to conquer. One of our major weapons, and for a long time our only weapon, was quinine, from the bark of the cinchona tree, aka Peruvian bark. By itself it is bitter to the point of utter unpalatability, so it must be compounded with something to make it "go down". A strong red Iberian wine was one good way to mask the flavor, making it, as the label says, "free from the disagreeable bitterness of other remedies". The Brits in tropical climes came up with their own solution, masking the bitterness by using gin, the popular alcoholic beverage flavored with juniper and other ingredients, and thus was born the gin-and-tonic.



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When looking at the broad panoply of wound products, new and old, they can all be reduced to just a few basic categories. Keeping straight which category a product goes into is very important to keep expectations about the product in proper perspective. Good products used for the wrong purpose will be perceived unfairly and negatively. Once you understand the real value and purpose of a product, even if it is quite different than what you first thought about it, you might find an unexpected gem. Most wound products fall within the following 5 general categories.

1 - Wound and skin management. These are the basic products that support wound hygiene, skin health, and the necessities of daily care. **Generic wound care** products are dressings and non-specific topicals that maintain basic wound hygiene, patient comfort, absorption and moisture, edema control, etc. **Purpose specific topicals** are those that serve the purpose of daily hygienic care, but also have some additional therapeutic or other deliberate purpose. These include materials that incorporate pharmaceuticals for controlling bioburden, inflammation, pain, etc. They include agents that have some nominal (but weak or poorly documented) stimulatory or pro-proliferative effect, such as those with traditional vulneraries or their purified derivatives such as honey, allantoin, and acemannan. They also include those that have some semi-regenerative effect to guide the growth of new tissue, such as those based on collagens or aminoglycans. **Skin care** products are those meant to protect the skin, heal non-ulcerated dermatoses, treat dermatitis, and care for special problems such as intertrigo and stoma and fistula problems, including protectants, barriers, moisturizers, and powders and antifungals. **Devices** are those that support the basic essentials of hygienic care, such as chemical products and gizmos for debridement, and substitutes for conventional dressings such as negative pressure devices (manufacturers would like to promulgate the notion that these devices are stimulatory wound accelerants, but first and foremost they are just another mode of basic hygienic care).

2 - Wound healing. These are products which are meant to affect the wound healing process by direct pro-proliferative effects on wound healing cells and their functions. In general, the wound management products listed in paragraph 1 are those required for phase one of wound care, getting the wound under control, and keeping it healthy and capable of healing. The wound healing products mentioned here in paragraph 2 are the discretionary items used to promote closure and get the wound healed. These tend to be sophisticated and technology based, and thus are expensive or have some other major investment of time, risk, and resources. Hence, the wound healing products should never be used until the wound has been controlled and rendered receptive to their effects. Wound healing products can be divided into two broad groups, stimulatory and regenerative therapies.

Stimulatory therapies are those meant to induce, stimulate, and accelerate wound healing, either returning retarded wounds to normal kinetics or accelerating wound kinetics beyond natural rates. They tend to fall into certain general categories. ***Platelets and platelet releasates*** are meant to concentrate the cytokines or growth factors which normally trigger or induce the whole wound healing process. They are available in a variety of technologies from many vendors. ***Purified growth factors*** are conceptually important, but other than becaplermin-pdgf (Regranex®), there are no significant products available. ***Living cell biologics*** have emerged as conceptually more important, in the form of living re-engineered tissue analogues which put living cells on the wound (usually neonatal cells from non-specific donors). The cells do not survive as allogeneic implants or grafts. They live for limited times and then degenerate, but while there, these young cells express a broad spectrum of pro-proliferative chemicals which have a stimulatory effect on the wound. They are best thought of as pharmaceuticals packaged in living vehicles. Apligraf® and Dermagraft® are the two common and worthy examples. ***Acellular biologics*** are non-living materials taken from biological sources. They are mainly fascias or other connective structures stripped of all cellular and antigenic materials. They depend on the chemicals or micro-architecture of their matrix to stimulate or guide host wound cells. Examples are Oasis® porcine intestinal submucosa (*Cook Biotech* and *Healthpoint*), and Unite® Biomatrix equine pericardium (*Synovis*). Dispersed or solubilized biochemicals, such as collagen and aminoglycan pastes can also be included here. ***Physical agents*** are those that stimulate repair by delivering energy or load to the wound via physical modalities such as electromagnetics and mechanics. There are devices to deliver radiofrequency (rf), lasers and other visible light photonics, electrical and electromagnetics (em), and ultrasound and vibrational energy (us). One of the perversions of medical science in the 19th and 20th centuries is that everybody got so focused on biological chemistry and pharma, and made organic chemistry the acid-test of medical school acceptance, that mostly everybody forgot about physics in biological systems. The consequence is that the scientific, clinical development, and regulatory processes for physics-based devices is not as elaborate or taken as seriously as anything that has a chemical in it, regardless of the medical subject or specialty. Wounds are no exception, and these devices do not get the attention and respect that they deserve, nor is the data and clinical experience and supportive science there the way they should be. Nonetheless, many of these devices seem to be very promising wound stimulants. ***Old pharmaceuticals*** are the vulnerary herbs and traditional remedies that have never made it into well studied and scientifically developed pharmaceuticals (slides 12 – 16). Too bad, because there is some promise in those weeds. Certain purpose specific topicals discussed in the paragraph above, such those with allantoin and acemannan justifiably fit into this category as well. ***Novel pharmaceuticals*** are a variety of items that get presented at major wound meetings and which are in scientific or commercial development in

labs around the world, but which have yet to appear as prescription products. Many of these items sound very promising when presented at meetings, so we will all just have to wait and see. One of the most promising of these novel forms of therapy, a biological approach, are the ***transfectives*** in which you "give the wound a cold", using safe viral vectors to introduce wound-proliferative genes into wound cells. thereby turning them on to grow and assemble. The current front lines of promising wound therapy research seem to be mostly within the realm of wound healing and wound stimulatory therapies. These pending products are biotechnologies based on living cell therapeutics and genomic-proteomic pharma. How they will work in clinical practice is yet to be seen.

Regenerative therapies are those which turn off normal post-inflammatory healing and instead induce embryonic or regenerative processes. Osteoinductive grafts and regenerative bone healing have been part of the landscape of surgery for many decades, and similar concepts that apply to tissues and organs in general, including wounds have become very important in the past 10 – 20 years. With regard to wound healing practice, there are several available products. They are mostly (but not all) made of biological chemicals or materials, generally in the form of a micro-porous scaffold or trellis. They are implants (even when applied on the surface) that are not alive to start with, but become so as autogenous cells find the matrix and form the new tissue. ***Regenerative skin substitutes*** are skin analogues that serve as "artificial skin" when applied to open wounds, getting them healthy, then serving as the scaffold upon which new dermis or epidermis can form. Integra® collagen-gag matrix is a good example. ***Cadaveric skin matrices*** are dermis or fascias from allogeneic or xenogeneic sources. They are stripped of everything but basic connective matrix (collagen, fibronectin, some gag's, etc.), and they are non-antigenic when properly processed. Applied to a wound, primitive cells find the matrix and initiate a process of stromal histogenesis that, entirely unlike scar, resembles normal embryonic processes resulting in the formation of new dermis or fascias. They can not only heal certain refractory wounds, but they can supplant many conventional wound repair operations, thereby avoiding autogenous donor sites. Many companies make competing products derived from human, porcine, bovine, and equine sources (Alloderm®, FlexHD®, Strattice®, Surgimend®, GraftJacket® to name a few). Many of these are promoted as wound healing or wound stimulatory products as well (e.g. Oasis® and Unite®, mentioned above) – the nomenclature and effects are not always well characterized, and these products can have both effects. ***Miscellaneous bioparts*** are the other bric-a-brac of cadaveric harvest, including miscellaneous skeletal parts for orthopedic reconstruction through whole organs for transplantation. Most of these are not intended for wound healing purposes, but understanding their biology of incorporation, regeneration, and possible atrophy, inflammation, or rejection is a good starting point to understand the biology of the wound relevant biologics. The one obvious cadaveric tissue of wound relevance is skin itself, and cadaveric skin banks have been in operation for many decades to support burn surgery. The role of allogeneic skin in the management of wounds is a fundamental in the basic arts and sciences of plastic surgery, and understanding this modality is important to understanding wound therapeutics in general. However, allogeneic skin is more suited to acute wounds, especially large trauma-burn-fasciitis wounds, whereas modern wound practice focused on chronic and pathological wounds benefits more from the various other technological products discussed here. The conjunction of skin grafts and technology also gives us the opportunity to grow autologous skin in vitro. Commercial services to do so have come and gone, limited by the costs and expenses involved, and these services likewise are mainly suited for burns.

3 - Patient support & rehabilitation. These are the products which assist your care and your patient, oftentimes larger items involving durable goods, systems and services, and personnel. They can range from crutches and walkers through splints, braces, and full extremity prosthetics, from wheelchairs and cushions to pressure relief beds, from colostomy bags to edema pumps to glucose monitors, from pharmacies to rehabilitation facilities to home health services. This is obviously a diversified group of items, and while you might not think of them in the same way as the "wound healing products", they are equally important, especially when it comes to wound prevention and general patient maintenance. Just see how far you can get with the wound care products if these support products are not there!

4 – Diagnostics. Diagnostic devices are becoming more relevant in everyday wound practice. As we become more sophisticated in understanding the chronic wound as its own disease, biotechnology is bringing us new tools for measuring and quantifying the wound and the underlying diseases. However, there are few standards or accepted relevant practices in the wound lab. Compare wound practice to other specialties and their tests: heart medicine (ecg, catheterization, pressures and flows, echo), pulmonary medicine (radiography, pft's), vascular medicine (angiography, imaging, and many forms of flow assessment), ophthalmology (ocular pressures, retina photography, refraction), and so on. For wounds, there are few tests of the wound per se, wound photography and linear measurements being the most relevant and prevalent. Even there, many attempts over many years to develop automated wound measures (area and volume) have failed, and a nurse with a ruler is still the gold standard. Most "wound diagnostics" are aimed at the underlying diseases, not the wound itself. Nonetheless, several of these technologies are quite standard, and you can expect to see more and more in coming years. There are a few items that can be considered standard practice at this point, even if not every practitioner or facility has them: the vascular laboratory and all of its gizmos, tissue oxygen or tissue perfusion measures (e.g., TcpO2, laser doppler), pressure mapping (for foot and gait, and for pelvis-seating-bedding), and the standard clinical lab (auto-immune and coagulation studies, histology). Young technologies worth keeping an eye on include wound imaging by multi-spectral image analysis, and wound proteomics and genomics via gene chips or novel laboratory panels.

5 - Ancillary therapies. There are many items relevant to wounds, and the rest can be lumped here. One example are the surgical devices and wound closure widgets. Surgery is crucial for the final closure for many wounds (and it has no role or is contraindicated for many others). Going beyond the trivial items (sutures, staples, glues, instruments, etc.) some surgical principles can be applied to everyday wound care in the form of mechanical wound closure devices. Meant for office and clinic use, these gizmos put mechanical forces on the wound, attempting to slowly relax and advance the skin margins. They are of mixed utility, especially when dealing with wound-healing-incompetent wounds, but they are an example of an idea that is sensible at face value. Another example is hyperbaric oxygen therapy, a modality which is relevant, useful, high profile and expensive, but which is not explicitly a wound healing technology and which does not fit into the other categories. Then, there is all the paraphernalia which supports the management of the underlying diseases which caused the wound, such as all of the stuff used for vascular surgery and for pressure relief and management. If you are in a chronic wound practice, then you will be barraged regularly with new items, some potentially valuable, some not quite ready for prime time, and some just simply "not", and you must make discriminating choices about which seem meritorious and which are bogus.

Competition or cooperation with other products. Many problems in medicine require sequential therapies as part of a coordinated program of care. A diabetic patient in hyperosmolar ketoacidosis needs certain acute life-and-death treatments. Once that is all stabilized, then he needs

proper diet and insulin therapies. A Crohn's patient with acute bowel obstruction or perforation needs life-saving emergency surgery. Once the acute phase is resolved, he then needs anti-inflammatory therapies and functional bowel management. Every problem or specialty in medicine has its Phase 1 of acute care and stabilization, then Phase 2 of discretionary care to resolve the disease and its sequelae, then Phase 3 of preventive care and maintenance. This is eminently true for wounds, Phase 2 being where discretionary treatments are applied to heal the wound once it is controlled of its acute ulcerative phase. However, this is not what we mean when talking about sequential therapies for wounds. The concept here is all within that discretionary Phase 2 where you are trying to heal the stabilized wound. The problem is that wounds come in all sizes and flavors, and they have various logistical problems in their care related to size, location, number of wounds, resources and personnel available to assist with the required care, patient disabilities, and economic resources. Some therapies work well under some of these constraints, others not, and vice versa. A product or strategy or technique or modality might work for only so long, inducing a beneficial change in a wound only up to a point. If it ceases to work or to get past a certain size of the wound, that must not be seen as a failure, but rather as the reality that certain products only work within certain ranges. It is not only appropriate, but the acknowledged general strategy in wound management that therapies can and should be used sequentially, one after another, each tactic being used within its own operating range, then handing off to the next modality or product as the wound gets smaller.

For example, imagine a large pelvic wound following some sort of trauma or fasciitis. Such wounds having surface areas of 1000 square centimeters or more are not at all uncommon. Assume that you have completely cleaned up all of the acute mess, the patient is now healthy, and the wound module has proliferated and is receptive to any type of wound healing or wound closure method you might wish to apply. In principle, skin grafts or other surgery might resolve much of the problem quickly, but for any number of perfectly legitimate reasons surgery cannot be done. However, to expedite closure, you will apply technological products meant to accelerate wound healing so as to minimize time and costs involved in restoring the patient to full function. What can you use? Becaplermin-PDGF (Regranex®, *Systagenix*) is one of the important stimulatory therapies, but it only comes in a 15 Gm tube, at roughly $1500 per tube. It is meant to be applied approximately 1 mm thick. So, 15 Gm is approximately 15 cc (assuming density of the gel is comparable to water), which sliced into 1 mm wafers gives you 150 sq cm coverage. So, you need 7 tubes to cover a 1000 sq cm wound, each day. You just broke the bank. Sorry, that option won't work. Well, what about Apligraf®, *Organogenesis*, a living neonatal cell biologic, another one of our valuable stimulatory therapies? Each circle of the material is 42 sq cm, roughly 1/3 or 1/4 of the coverage of a tube of becaplermin, for roughly the same price, although it only needs to be applied every week or two. Still, the costs of these modalities on such a large wound will be comparable – way too much. Even if cost was not an issue, the sheer physical logistics of applying those materials properly and holding them in place the requisite time is a challenge. So, what does work for large wounds like that, easy to use and cost effective at those scales? We have products for large scale, starting with the rudiments of good hygiene and basic cost effective topicals. If we want to stimulate or otherwise actively affect that big wound, and do so realistically and economically, we can do so with radio frequency (e.g. Provant®, *Regenesis*), or with negative pressure therapies (e.g. VAC®, *KCI* and competing products), or with ultrasound (e.g. Mist®, *Celleration*), to name a few. What happens next when the wound has contracted to perhaps only 50 sq cm, but it has stalled, no further progress for the past few weeks? Time to switch to something else. What now might be a bit more potent and specific and suitable for the current size? Apligraf® (*Organogenesis*) or Dermgraft®, (*Advanced Biohealing*) would be good choices now. And what if after 8 weeks of therapy the wound is now just 5 sq cm, but no more progress is happening, and these modalities no longer seem to have an effect? Becaplermin-PDGF would now be a good option at this small size, very cost-effective, yielding 30 days of therapy at current wound size, but actually 60 days of therapy since the wound will be getting smaller, enough to carry it across the finish line. (Remember, the use of proprietary names and products is not to be misconstrued as explicit endorsements, and no one has paid me anything to put their name in print. On the other hand, these are the real products we really use because they really work and let us get our patients fixed up. There are many other products as well, and you can use the concepts of this section to find the time and place for your favorite products as well.) Also, anywhere along the way in this case scenario, surgery could be done to close the remaining wound if appropriate, and if the above therapies have reduced wound size leading to smaller grafts or flaps or less post-operative morbidity or recovery time, that too is valuable. The principle of tandem or sequential therapies is very important in wound practice, and many products from many of the categories above may ultimately be used over the duration of care for any one wound.

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Integrating New Products and Technologies into Practice #6

Guidelines for assessing new products: product utility & relevance.

There is both wheat and chaff among the endless new products, and sometimes there comes along a genuinely nutritious and tasty grain that will fundamentally change they way you and we all do things. All practitioners are obliged to keep an eye open for them, and hopefully participate as well in the planting and harvest, i.e. the trials and evaluations, the reporting and education.

For any new product or concept, you can choose to wait and hear the recommendations of other users, or you can take the initiative to be one of the first to evaluate a new product (and then be the one to communicate that information to others). Either way, you will have to discriminate good from bad, real from bogus. The rest of this presentation is meant to give you some guidelines for separating the wheat from the chaff.

The products that support wound practice have a wide range of relative value and importance. Some are vital things without which we just as well might be living back in the trees. Others are strictly non-essential luxuries, and there are others genuinely valuable but needed just once in a blue moon. Some are too expensive or non-pragmatic to be used much, while others are good enough to supplant whatever else you used to use. When looking at our supply cabinets and procurement paperwork, products seem to fall into four general categories, and you can be sure that every new item will fall into one of these.

1 – Trinkets: baubles & bling in the supply cabinet. These are the items that sounded good when you decided to try them, but the shine tarnished quickly because they do not really work. Or else they work well but have very few eligible patients, or they work well but have all kinds of administrative headaches that keep them from being practical to use. They may involve some monstrous piece of equipment that impresses visitors but eats up valuable space.

2 - Toolbox toys: special items that you know you will need infrequently, now and then, just in case, but when you need them you really need them. Any dude who has a shop, who does woodworking or rebuilds cars knows about this one, that special wrench or riffler that you know you will use just once in 10 years, but your toolbox would be incomplete without it.

3 – Trailblazers: changing the way we do things. These are the revolutionary things that change the fundamental ways in which we solve problems and accomplish tasks. Anything that you use daily and take for granted was once a novel concept or product that had to prove itself in practice and in the marketplace. Some advances are overt and obvious and catch on immediately, such as the use of ether and anesthesia in surgery after its first use in 1846. Others are not so obvious or else meet resistance to new ways, such as the 30 years it took for Listerian antisepsis to become normative practice in surgery after its first publication in 1867.

4 – Workhorses: the products you really use everyday. These were once new and novel, and in their own day they first met acceptance or resistance. Today, you hardly notice them even as you use them daily. Imagine how your practices would change if cotton gauze or scissors suddenly disappeared, narcotics or anti-inflammatory drugs, ecg's or computers or telephones or electricity itself. The trailblazers and workhorses do not announce themselves. The marketing men behind every new product will make that announcement for you, but the real value of genuinely valuable products awaits to be discovered by you.

5 – What if's and the wishlist: Yes, we have many wound products, important or not so, used daily or rarely, highly effective or so-so, but all real, tangible, and generally easy to procure. But in this business we are always looking for that other item, the one that works better, the one that gets better results, the one that is easier to use, the one that solves that special problem you have right now. In the quest for new and better, it is worth considering the betas, boneyard items, vaporware, and other fantasy products of this business, the missing products, what-if's, and wishlists, because there are some nuggets to be mined there. First, consider those products that (1) do not exist, (2) did and died, (3) live in oblivion, (4) could or should be developed but no one has. As examples of such products, consider three that incorporate allantoin, acemannan, and hyaluronic acid.

Allantoin (5-ureidohydantoin) is common in nature, the final water soluble endpoint of purine metabolism in almost all species. Just a very few species, including man, lack the enzyme to do the final conversion, meaning that our purines degrade only to marginally soluble urate, giving us the gout. In the classical European materia medica, the comfrey, Symphytum officianalis, has always been one of the most potent and preeminent vulnerary herbs. In the early 20th century, comfrey root was found to have an unusually high concentration of allantoin. In a seemingly unrelated thread, many had observed that maggots, fly larvae, which were commonly found on untreated putrefied wounds seemed to expedite wound healing. In the 1930's, those studying this effect observed that the improvements were greater than could be attributed to fly "munchies" mechanical debridement. In studying the issue, the benefit was discovered at the other end of the maggot, with high concentrations of allantoin in the fly excreta. In 1976 in the Archives of Surgery was a report on a medication compounded of silver ("A" for Ag, for its anti-microbial properties), zinc ("Z" for Zn, because its presence in skin was an in vogue topic of the day), allantoin ("A", for the threads of evidence just mentioned), all prepared as a cream ("C", for topical use). The AZAC paper showed some nice results healing some chronic wounds. Allantoin is the perfect example of a classic vulnerary chemical of genuine potential significance that has been overlooked by serious researchers and corporate development over the past century. It is easy enough to hypothesize that as a degradation product at the end of a major metabolic pathway, that it would have some sort of promotional or inhibitory feedback on antecedent steps in the chain, thus having useful pharmacological properties, be they for wounds or otherwise (especially in allantoin-naive species where the feedback might be strong due to the absence or attrition of any modulators or dampeners). Allantoin deserves proper study and development. However, the lack of intense study and academic rigor did not dissuade at least one company from trying to make a modern day allantoin-based topical wound product. Carrington Dermal Wound Gel, made by Carrington Laboratories, has now been on the market about 15-20 years. It is a "second tier" product. It gets little attention. The company does not even seem to have a website that works. They seem not to have any reps that visit doctors and hospitals. I do not know what regulatory level it is subject to with the FDA, but it seems to be sold more as a non-specific topical, more of a skin care item than a pharmaceutical. Is the lack of a serious market or marketing effort based on the deliberate strategy of the company about this product, or a blasé disinterested attitude, or a pragmatic choice based on regulatory effort versus costs and efficiencies? I don't know. Twenty years ago, it had some fanfare, now nada. Is it a good product? I don't really know, since it is not available to us in our purchasing contracts for basic everyday products, we have had prescriptions rejected by pharmacies as non-available or non-formulary, and any of our patients who want

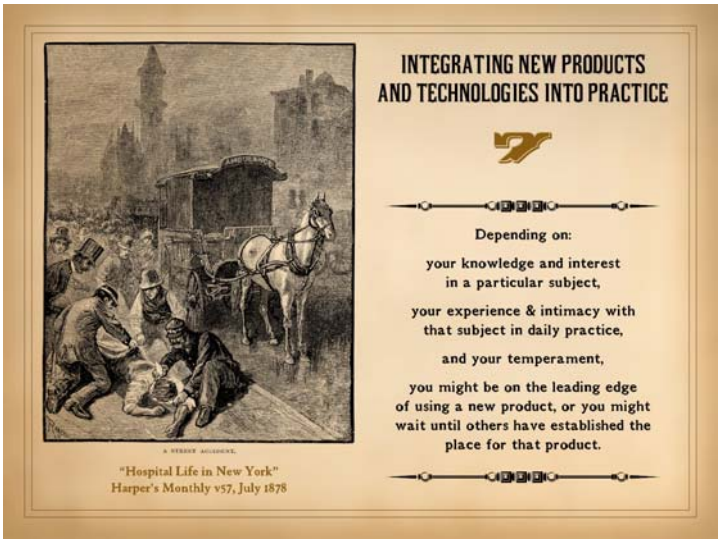
to try traditional vulneraries can get more potent forms as comfrey extract in health and natural food stores. The lesson here is that if there are products which make sense, try to use them and create a stable supply source. Speak to manufacturers and get them to give you samples and experiment for yourself with what works. Ask the pharmacies to stock it. Have a reliable second source or backup, which for allantoin is comfrey extract (or modern day medicinal maggot therapies, which are commercially available if you, your staff, or patients want to use them). What if . . . what if somebody had ever properly studied allantoin? Perhaps we would have a genuinely potent wound stimulatory therapy in proper concentrations, properly marketed and available for effective use.

Another what if example is acemannan, a polysaccharide that comes from Aloe species. Aloe vera and other aloe species have been used as topical burn and wound dressings for a long time. In the traditional materiae medica, it is not so much a true vulnerary that makes wounds heal, but more of an anti-inflammatory that settles the acute phases of acute wounds, especially useful for burns. Either way, aloe has received attention off and on for as a potential product for wound care, and quite a lot of its candidate chemistry has been studied. It has a variety of useful chemicals and therapeutic properties, including acemannan which, in the early 1990's, was focused on for mitogenic and proliferative properties of potential value for wound healing. It was used by Carrington to make Carrasyn gel, a topical wound product. I always thought that this company was on the right track, looking at conventional phyto-chemistry in a search for vulnerary pharmaceuticals. Remember, in 1990 "biotechnology" was an incipient industry of high hopes and modern technologies but uncertain market value and practical utility. But it was the bandwagon that everybody wanted to ride, and as it has come to fruition, the focus and methods and market products are generally focused on complex chemicals, recombinant technologies, genomics and proteomics, and other such cutting edge technologies that ambitious company execs and scientists learned as grad students and post-docs, and which are glam and get chi-chi funding. Even in traditional pharma, the focus for the past 40 years has been on designer drugs culled from giant catalogs of synthetic organics which can be patented for the patent-and-profit corporate model. Classic crude drug pharmaceutical chemicals seem to have become orphaned step children of trivialized irrelevance. So, any concept or vision that a Carrington might have is likely never to be fully realized. In part, a company like Carrington has to fight against the preponderance of time, attention, funding, effort, personnel, and research that more cutting edge au courant technologies get – i.e. their failure is not their fault, just bad timing and society. In part, to be successful, their phyto-vulnerary topicals needed good marketing backed by some compelling research or data – right-upper on the bogosity matrix – legitimate but with limited data. As a topical wound dressing, the regulatory requirements are not so stringent, so good studies are not so crucial. Thus the allantoin and acemannan products fall into a trivialized product category, and most people are unaware of these products. Do they actually have a legitimate vulnerary effect? Should they be great products in wide use? That is impossible to answer, because meaningful data never accumulated – but in principle it should have. For products like this, a great study would incur a rather simple efficient protocol that would make the study inexpensive (as studies go), and which could be done quickly for hundreds (even thousands) of patients at multiple centers with several investigators – a great study that would answer the question, opening the market to these safe, accessible, inexpensive products if they proved to be useful.

Another example, but different, is a product named Hyalofill, from Convatec. It was on the market for a few years, but no longer, but possibly returning one of these days under different proprietorship. Hyalofill was marketed as a wound dressing. What made it unique was that its active ingredient was hyaluronic acid. I cannot recall what if any were the special marketing claims and usp's (unique selling points) for this product, but as I recall the claims were somewhat nebulous "rah rah wound healing", like so many other products, with some vague and not-very-technical-erudite-informed-meaningful explanations of why hyaluronic acid might be important or worth your attention and prescription. So, the product fizzled, then died – off the market. It has since been bought by an investment group that promises to develop and remarket it. The problem with entrepreneurial holding companies is that they suck up a portfolio of products, good, bad, useless, and potential gems, but not being clinical-science-technical people, they often have no real idea of what the product means, why it is good-bad-otherwise, and no special plans to do anything with it anytime soon – good patents and manufacturing processes locked up and wasted in limbo. I have had discussions with the new company, with promises that they would speak to use, all enthusiastic that someone is interested in their shiny new bauble, but they have made no followup nor further contact. So much for entrepreneurship and the proverbial "hungry young company". Why do I want this? Why should this product have remained with a reputable, experienced, resourceful company like Convatec? Why should you care? Because hyaluronic acid, as one of the matrix gag's (glycosaminoglycans) is one of the most profoundly important chemicals in embryonic histogenesis, control of inflammation, and the healing of wounds – one of the key agents that governs the execution of the embryogenesis-regeneration subroutine versus the inflammation-proliferation subroutine. In theory, hyaluronic acid and its sister chemicals (uronic, chondroitin, heparan, dermatan, etc.) should have a profound beneficial effect on promoting the healing of the hardest-to-heal wounds. The problem is that nobody has really studied it very much as a wound healing entity. For reasons related to history, happenstance, the hegemony of the pedants and pedagogues running graduate studies, neanderthal love and other anachronisms, and other reasons related to lemmings and bandwagons, everybody, from academics to corporate execs to biotech inventors and investors, everybody has gotten focused on collagen as a the must-have me-too everyone-else-is-doing-it biochemical wound product. As a wound healing product, pure collagen makes some but little sense. As a composite material with fibronectins and other smaller matrix proteins it makes more sense. As a yet richer material partnered with gag's, it makes even more sense. And what about gag's alone? Who knows, but they probably have a greater potential role in regulating good wound responses that collagen does, and the product vector ought to rotate toward the gag axis. Why? The gag's are part of the general ground substance. In the embryo, traumatic injury does not induce inflammation and fibrous healing, just a re-accumulation of ground substance gag's and continued embryonic histogenesis. On slide 4 the product Integra was mentioned (and to be discussed in greater detail on slide 35). A huge amount of information is available on this product at the arimedica.com website, including a complete discussion of the histogenesis of the material. Its ability to eradicate inflammation and then trigger the embryonic transformation of histo-progenitor cells is largely due to the aminoglycan in the material (chondroitin). Having a properly researched, engineered, and manufactured aminoglycan wound cover would probably be of profound significance for the sake of controlling the effects of primary disease, the effects and persistence of acute inflammation, and the ability of regenerative cells, mesenchymal and epithelial alike, to proliferate, migrate, then reorganize and reassemble a new tissue, i.e. heal" the wound. Hyalofill never made it to success because it was conceived of and marketed as a dressing, not as a wound regulating biologic as it should have been. It failed because the company and all the lemmings were so focused on collagen and cytokines and silver and alginates that the product was never properly scrutinized nor reassessed from a science point of view, nor re-manufactured and re-branded as a properly investigated wound healing agent. We do not need more collagen wound products. We hardly need any at all – topical exogenous collagen by itself just isn't that important to wound healing. We really do need aminoglycan wound products, but now we have none. The company bailed, flipping the "asset" for cash, instead of holding and rethinking it. If they had held it, they at least had the in-house resources to re-research this if they chose

or could be persuaded. Now, it is in limbo. Too bad. Opportunity lost. Maybe if somebody who reads this has the will and wherewithal to make an aminoglycan wound cover, he can be our hero.

On the what-if's and wish list, we also have products pending, promised to be coming soon to a store near you. So they say. So we have heard. The wound meetings, the big national and international ones, especially the science-industry-technical ones are where you will hear the most about items being commercially researched and developed. There are many lines of investigation and development. Some never become tangible. Some get hung in regulatory purgatory. Some actually come to fruition. There are many concepts. The pending products that I have most been looking forward to are the transfectives – giving your wound "a cold". In this approach, safe viral vectors (e.g. adenovirus), doped with a therapeutic gene such as a wound proliferative cytokine, are used to inoculate native in situ cells. Preclinical and early clinical work looks very promising. I am not right now (2009 -2010) personally aware of where it stands, how close to market reality, but this is one concept worth looking forward to. What is the message for you, the discriminating purveyor and prescriber of wound treatment products? Without the products that some company makes, good concepts do not come to life. Without a company to sustain a good product, it dies. When end users know something that the company should but doesn't, users should speak up for good products, voting with your emails and phone calls to company reps, or else with your prescriptions to buy and use the products. Sometimes good companies with good products just have the wrong idea about it and need to hear the "real scoop" from YOU (see slide 34). Whatever product you use, do not just use it blindly. Try to understand what it does, why, and where it fits in the spectrum of products available, ready to be used whenever needed, whether that is every day or just once in five years.



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Integrating New Products and Technologies into Practice #7

Guidelines for assessing new products: general framework of evaluation & adoption.

You and your relationship to a new product will depend individually on you and the product. You might be on the leading edge of using a new product, or you might wait until others have established the place for that product. This will depend on your knowledge and interest in a particular subject, your experience & intimacy with that subject in daily practice, how much you might have known about or anticipated the product before it was available, and of course on your overall general temperament and approach to such things.

A street accident. From "Hospital Life in New York", Harper's Monthly v57, July 1878, and article describing the then contemporaneous advances in hospitals that turned them into the institutions that we have today (see slide 3). Part of the emerging civic hospital systems were the resources to pick up sick and injured patients and bring them to the hospital, with its receiving wards, nursing units, pharmacies and dispensaries, and operating rooms. Your use of any new product in medicine need not be a mad dash to be first-on-the-scene of new users. Your adoption of a product can be orderly, systematic, and thoughtfully reasoned after hearing the advice and experience of others. On the other hand, you have an obligation to be familiar with what is modern and newly available so that you are not the last to hear about something of genuine benefit to the people you treat.

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Here are some points of philosophy to guide your spirit in the evaluation and use of new products.

1 – Be educated and resist bogus claims: This is your primary hedge against disreputable practices by vendors with bogus products who, solely for their own remuneration, take advantage of you at the disadvantage of the patients who have entrusted in you. If you want to be a cardiologist, be a good one. If you want to be an orthopedist, be a good one. We have a system of formal specialty education and board certification that has various checks, balances, performance milestones, and peer examinations to ensure that in the mature specialties, that graduates can do what is expected of them. For wounds as a specialty, the same rigor and discipline just is not there yet. Most people who have voluntarily joined this specialty have the right morals and motivation, but absent a well defined curriculum and respectable academic departments, the technical knowledge and skills of wound practitioners are very variable and oftentimes not very expert. Anybody who cares to be in control of their own judgments on behalf of their patients, and not be hoodwinked by a company with a bogus product to sell you, has a few intellectual obligations. You must – must – understand wound science (anatomy, physiology, pathology) and you must understand the clinical arts of wounds (diagnosis, therapeutics, management). Even in the wild and wooly West of Wounds, maintain your equanimity, your intellectual composure, your professional standards of evaluating and using new products. Even when you are unfamiliar with the concepts and background knowledge behind a new product, there is always time to learn and then make an informed

assessment. Don't let patent medicine practices sway your thinking.

2 – Intelligently try new things: There will be times when promising new products all seem to arrive on the scene at the same time. You might decide that you want to try them all. Perhaps you even try each one one or two times. And then you realize – you cannot possibly develop expert insights about any one of them if you are using all of them. They might be similar products, or they might be very dissimilar (e.g. a topical peptide in a cream versus a surgical skin substitute) but for the same purpose of getting the wound closed. For any single wound or patient, you will get to use one or the other. Anecdotal use of all such new products is worthwhile to "get a feel for it", but not if you want to see which ones really or work or not, nor how to get the most out of a specific product. To master a new product, you can only get good with and understand a few at a time – maybe even just one if it represents a major new change to your overall practices and strategies. Ultimately, complete mastery, even complete awareness of all new products is unrealistic – actually, impossible. Thus your goal must be not to master everything, but to judiciously pick and choose things that seem most promising, that most closely fit the needs of yourself and your particular patients. Like every skilled craftsman, you must outfit and master YOUR toolbox. What is in your toolbox might differ from your buddy across the hall, or across town, country, or the whole world, yet your results might be equally good. And if anybody's results are superior, then the value of the relevant products can be learned at the professional symposia where knowledge and experience exchange and intermingle. You must be practical. Give promising new products an honest safe "test drive", then focus on those few that you can make a serious commitment to understanding.

Don't be afraid to "pull the trigger" for potent or risky therapies. In medicine, we do serious potentially lethal things to people because we have learned to manage the risks and complications and get the results. When we induce cardioplegia on mechanical bypass so we can chop out and replace a bad mitral valve, we are doing very unnatural things – but we do it, and successfully. When an oncologist gives lethal poisons in metered amounts explicitly to destroy your bone marrow, and thereby put you at risk for deadly infection, so that he can then replace your cancerous white blood cells, that is serious stuff. But we do it, and we do so successfully. Most wound therapies have not quite so much drama, but some do – if I excise all the skin and fascias for a bad burn or necrotizing fasciitis or primary lymphedema, I do so because I know I can then rebuild the skin. If I use cyclophosphamide or tacrolimus or an anti-lymphocyte mab to cure out-of control lymphocytic ulceration of the skin, I am taking risks, but I know how to manage them, and the good consequences of careful management are equally important for that patient as the mitral valve and bone marrow transplants were for their respective patients. If a new therapy seems potent, risky, strange, that is the reality of looking for newer better treatments. No one other than YOU is going to figure out how to use it and make it work safely and successfully. If you are a nurse or physician, then you have the license to prescribe or administer and manage the product and start figuring it all out. Unless you invented the product or are involved in pre-market trials, then if it is on the market it has some safety certification and "instructions for use". If your are the investigator, use your professional skills to figure it out for everyone else. So, don't be afraid to use new products – but use them wisely and carefully.

3 – Share knowledge: As implied above, real progress happens when everybody is trying different products, or different angles on the same product, then they get together and share the news. Share your experience and insights with others – via discussions, meetings, publications, whatever. Likewise, learn from others who are doing the same thing with the products they are trying – make a commitment to go hear them speak, at a dinner meeting or a major symposium or in a journal article. This issue is addressed more on slide 47.

4 – Do not adopt newness for its own sake: We are all on a quest to find the best tools to do a serious job. Tools – not toys. Toys are beguiling. Toys are fun. But toys do not get the job done. There is always a bit of the "new toy" mentality in playing with a hyped up new product, even more so when the product seems categorically different than extant therapies. The companies that invest huge monies in development and marketing, who have more fealty to their investors than their clientele are always going to try to "upsell" you to their new, patented, expensive, high-margin item. Their marketing staffs get paid to persuade you that new is better, and no strategy, from boys-with-toys to free pizzas delivered by sexy reps to any other bogus inducement is necessarily beneath them these days. New can be good – we are all always looking for something new-better. Sometimes new is good, sometimes great, and bit by bit we make progress and get better results with better tools. But new is not always good, and sometimes new is okay but not ipso facto better, and often old is better. In fact, many old products are uncontestable paradigms and foundational therapies. In recent studies, it seems that classic thiazide diuretics are often just as effective for controlling blood pressure and edema as the whole bevy of new drug classes that have appeared over the past 30 years. As the monoclonal antibody therapies have become accepted and are receiving ever wider indications and new compounds, we are now seeing a resurgence of interest in old standby anti-immune drugs, such as azathioprine and especially 6-mercaptopurine, as the very serious toxicities of the newer wonder drugs become apparent. As antibiotic resistance becomes an ever increasing cause for media sensationalism and death-and-doom sayers, it turns out that after three generations of conceptually different antibiotics, we are now seeing a return to safe and effective use of classic safe first-round agents, such as the use of tetracyclines and sulfa to dependably control (even the "resistant") staphylococcus. Remember, the company is always going to try to sell you the glitzy new model, because their principles and "morality" these days is often just the "bottom line". Nobody rightly wants clunkers of old products that do not work well, and nobody expects you to stick with the old when it is inferior. But even when the old is far superior – safer, more effective, cheaper – the companies are going to sell you what's new – because that's how they make their money and meet investors expectations – and you have no choice, because you can only buy what they are selling. And "they" with high profits to protect are the ones with big budgets to come visit you in your office to persuade you. The guys with the cheap dependable old products, the after-market guys, the bulk manufacturers who sell to the brand label OEM's, the off-patent generic makers and suppliers, they do not EVER, never will come and visit you in your office with a nice looking rep, a warm pizza, and a free imprinted ballpoint pen. There are great new products that you legitimately buy. Then there are others where, "baby, you've been sold". Equanimity – maintain your composure in the face of the sexy sales pitch. Tools, not toys. Never forget all of the old stuff that worked, worked well, worked safely, and keep using whatever is best, not whatever is new.

5 – Remain in charge of your analysis: The predicates to this paragraph are the four items above, The conclusion is that you can only buy what "they" are selling. What "they" are selling these days often has more to do with recouping big investments and making profits, more so than serving the public and their clientele. You are not being actively sold on old products without patents and profitability. The whole system is rigged towards using what is new, rather than what works. To reiterate, there are many great new game-changers, but it remains up to YOU to discern the good from the bad, to promulgate the good, and to ignore the bad until it goes away. As an evaluator of new products, you should

never just "jump on the bandwagon" because some pied piper has promised you a trip to enlightenment, nor because of "popular delusions and the madness of crowds". At all times you must remain in charge of your own psyche and intellect, your own trials and conclusions. Always beware of profit motivation and inept misleading marketing materials – because know it or not, you are being sold. Your own knowledge and principles must always trump sales pitches and fud. Likewise, you should embrace well reasoned and effective new items, or at least be open-minded, thoughtful and analytical, and give them a try. Your assessments, conclusions, and eventual everyday practices must be based on all of the virtuous things that you must bring on behalf of your patients who entrust their lives and well being to you. New for its own sake is not an inherent virtue. Do not be so enamored of the new that you forget your old friends. Keep in mind the total value of the new and old products – cost, utility, effectiveness, safety – and choose wisely. All good tools should find a place in your toolbox, ready for service when it is the best tool for the job.

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Integrating New Products and Technologies into Practice #8

The bogosity matrix and individual product assessment (including case studies).

How do you judge the technical merits of a new product? New products involve many details of chemistry, physics, engineering, materials science, math and statistics, bio-interface and transduction, computational and human interface technologies, and analysis and presentation, not to mention the core biosciences behind it all. In our complex society with its intricate systems for developing and using products, one must likewise be familiar with the sociological aspects of how a product came to market, including some business-finance-marketing, and then the government-regulatory-legal aspects of it all. Physician education is predicated on the principle that all physicians have a sufficiently thorough undergraduate then medical education that they can be conversant on these subjects and cannot be seduced by the misleading claims of disingenuous salesmen. Even so, these are big subjects, and no one can be so thoroughly familiar with all of these subjects that every new product for every purpose can be fully understood and critically evaluated without some new education or explanation.

Practitioners must evaluate new product claims based on several technical criteria, including: purpose and need, efficacy; proven or promising science; safety, risk versus benefit; utility and cost, comparative value. Given the reality that no one can be totally conversant or skilled or expert in the many disciplines listed, given that you will be asked to assess new technologies and products that you might have little familiarity with, how can you take the knowledge you do have, mixed with your plain old common sense, and make an intelligent evaluation? It can be done. The next few slides should help you decide when there is a "red flag" warning of a bogus product versus a meritorious product. We will start with a checklist of questions and items to be answered for each product, and then we will learn how to use the "bogosity matrix".

An advertising cut from The Household, volume XXV, 1892, a nationally distributed women's monthly magazine published in Boston. As described on slide 15, this era saw all manner and make of electromagnetic novelties to cure what-ails-you, including Dr. Bridgman's full power Electro-Magnetic Ring. Wearing a ring next to your achy joints was sure to sell to people with rheumatism. It also cured gout, sciatica, neuralgia, numbness and blood disorders, and other things, and it came with all of the implied testimonials that one could ever ask for. On slide 16 we looked at Henry's Carbolic Salve which was a pseudo-legitimate product for its day, an incorrect product for reasons innocent and understandable from the perspective of that era. The electro-magnetic ring was a bogus product, even in its own day. It was the perfect fad-fud device, using the technological buzzwords and romantic developments of the day to prey on your fears for your own health and life. It was strictly bogus, because although electro-magnetism was a hot topic of the day, just like carbolic and antisepsis, this product had absolutely no foundation whatsoever in any science nor investigative research nor proven technical or clinical development, nor did the customer-sucker have any way to verify that this monolithic piece of jewelry, plain or gold-plated, had any magnetic properties whatsoever. You bought it on good faith from bad faith hucksters. It was bogus, and a little thoughtful analysis would have led you to that conclusion.

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So far, we have been talking about general principles and guidelines for evaluating or working with new products, conceptual premises and an ethos for good practice. Now, we will start to focus on the assessment of individual products. Regardless whether you are evaluating a drug, a device, a new operation, a new therapeutic protocol, or anything else, the questions you should ask fall into five general categories.

1 – Concept: What is the purpose and rationale? Does it fulfill a need? Does it make sense? Does it solve problems or fulfill needs for my patients, because current therapies are not good enough? Every product is conceived by its author or inventor as something useful, but that does not make it so. Unfortunately there are products where the inventor has a technology or an invention searching for a use, but no direct expertise or experience in the subject or target audience. In recent years, there have been quite a few here-today-gone-tomorrow wound products where a naive inventor and his entrepreneurial investors should have spoken first to a genuine expert and more accurately assessed the potential utility and technical merits of the product. There are also products that go the other way, big winners where the naive or single-minded technologist stumbled onto something that no one really understood, but once it is on the market, it has value and applications beyond what anyone might have guessed. The moral is that you must keep an open eye and ear to vague and unforeseen possibilities, but still, the product must have some degree of conceptual utility or necessity before it gets your serious attention. If the company representatives cannot themselves explain the value, it will never win and is not worth your time. However, if the justification seems sound, even if completely novel, pay attention.

2 – Proof: Is there valid science, proven or promising? Does it fit with what is known? Have satisfactory clinical or other real world trials and evaluations been made? What were the testing protocols and analysis? Is it efficacious – does it work – in the lab, in clinical trials, or anywhere else? Is it safe? Good ideas are cheap. Getting a good idea to tangibility, or further yet onto the market, should garner admiration and respect for anyone who has accomplished it, because it is not easy and it is not trivial. But that does not automatically mean that the concept or new product actually does anything. If you are to take it seriously, there must be some evidence that it actually does what it claims, or anything else useful. Recall what was discussed on slide 14, that many wound products and "trials" or "studies" confuse simple hygienic care and the restoration of natural wound healing kinetics with genuine therapeutic effects to accelerate or positively promote wound healing. Sadly, there are many wound products that make it to market with good faith but utterly naive and inept studies that make it past unsophisticated and indiscriminating eyes. (Until wounds are no longer such an undervalued subject in the medical curriculum, reviewers, regulators, and other gatekeepers in the broader arena of medical products will continue to get duped or make erroneous judgments about what really works or not). Remember, all new products are going to have limited supporting data, so good proof or data are not make-or-break discriminators. That is why "good concept" is also important, even more important in the earliest phases of development. Somewhere within the scope of good concept and good proof, there must be something to win your respect or attention. If not, then the product may be bogus. Safety is also a proof-of-concept issue. Regardless of how theoretically useful something might be, if it cannot be used safely, it cannot be used. But, do not categorically dismiss a nominally dangerous item until you understand more about it. Crucial tools for medical practice include cardiac glycosides, cardioplegia, neuromuscular blockers such as curare and botulinum, and organ transplants and blood transfusion – all lethal if used improperly, yet all done everyday because we know how to regulate and manage the risks.

3 – Principals: Who is the company? . . . who is behind the product? . . . are they reputable or credible? Who represents the company? . . . how well? . . . can they adequately answer your questions? How do they do business? . . . how is their customer liaison, support, feedback, and interaction? Is this a credible company that you can believe in? Some products come from big experienced companies that you can trust. Some are coming from big experienced companies that have gotten some black eyes lately and deserve your wariness. Many products are coming from small startup companies that have no track record. "Good concept" and "good proof" are thus the important credentials. Nonetheless you still need to know that you can trust the company to support your use of the product, to keep you informed, to give you accurate honest information, and to be around to continue making good products. Ultimately, the most important principal or stakeholder is you, because if you do not speak up against bogus products, or if you prescribe and use them for fallacious reasons, then a disservice is done to your patients and society. Likewise, if you do not prescribe or properly use worthy products, then good tools that we might all depend on risk going away.

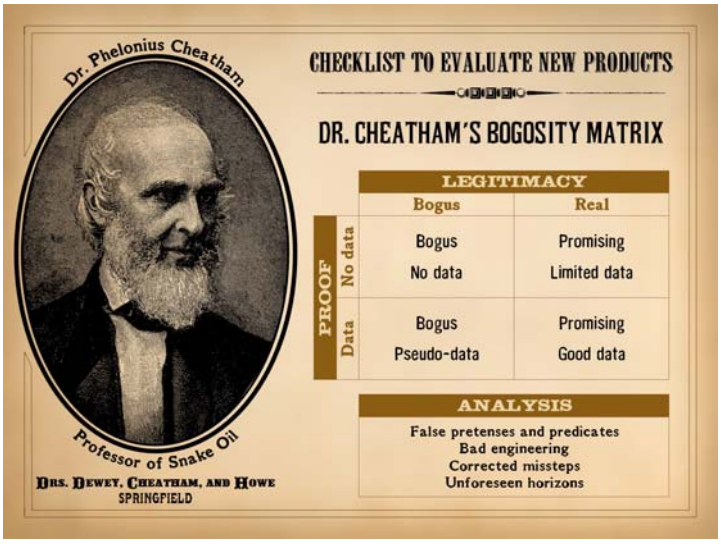
4 – Principles: Is the product or company driven by science-biotech, clinical-medical, or business-marketing? Are the marketing materials meaningful? Who is the target market? Are you dealing with real reps or with pitchmen? Are the scientists and executives accessible? Are they dazzling you with legitimate brilliance, or are they muddling with manure? Every company is going to have some set of core values and ways of doing business and ways of presenting and representing themselves. Does it all seem reputable and dependable to you? You would think that any self-respecting person or company that wants your business would pay attention to the details of how they interact with you, and most do, but some do not, and I find it hard to take them seriously if they do not take themselves seriously. Even with great companies and products, you need to understand their motivation. If the product impetus comes from clinical-medical people, it is most likely to pass the "good concept" test. If the impetus comes from non-clinical biotech inventors, the product might need more time for you to understand, and it might even be a major game-changer, but it might also be an irrelevant product with no real utility, even if technically competent. There really is a difference between products championed by the clinicians who directly appreciate the need versus those invented by inventors who could and then must seek an indication. Then, there are those products championed by (overly)-hopeful investment entrepreneurs and company executives where the motivation is monetary, sometimes with complete disregard for how irrelevant the product might be. Do the companies care enough to have the

product properly represented? Young companies on shoestring budgets might have no choice but to use rep companies rather than their own hired staff, but either way, a good company with a good product should be able to figure out how to present the product properly with relevant information. I have found that when good reps for good companies and products cannot answer you questions, they will get you connected to the scientists, inventors, company executives, or other clinician users so that you can get the answers you want. Remember, good concept is always crucial, but in the early phases of any product, even the best products, good proof and robust information might be scant. In those cases, good principals and good principles can be equally important to your assessment and willingness to try a new product.

5 – Value: Is a product efficacious? Is it safe? Is the risk versus benefit profile favorable? . . . likewise for cost versus utility? What is the real value of the item, and what is its comparative value against similar products or options? If a product neither does anything useful nor is safe, it is of no relevance or consideration. These criteria are so obvious and fundamental that they are the two paramount criteria for market approval by the US FDA. Risk-versus-benefit (bio-medical issues), which includes cost-versus-utility (socio-economic issues) are relative concepts. The more morbid or lethal the disease, the more risk we are willing to accept to get the job done. Does a new item have value sufficient to make you abandon tried-and-true methods and products? Are there moral or legal issues when companies offer inducements to switch that are not based on the intrinsic merits of the devices or drugs? (Yes, of course there are.) You, and only you can make these assessments on behalf of your patients.

Here are two examples of net value from the annals of medical manufacturing. Some of the earliest of the modern patent-and profit pharmaceuticals, in the 1970's, were the cephalosporins, then H2-blockers, then non-steroidal anti-inflammatories, then beta-blockers, etc. Most of these are me-too products that offer no real advantage over any other in class. In the 1970's, pepperoni-and-cephalosporin was the preferred flavor of pizza in doctor offices, clinics, and hospitals everywhere. All physicians would deny that they were swayed by such attempts to induce prescriptions or brand loyalty. Whether they were swayed or not, the blatant over-the-top abuse of this practice eventuated in some changes. Make no mistake about . . . if some company wants to buy you a casual dinner or give you a logo-imprinted coffee cup in return for your time and attention to hear about a new product, that is fair. Regardless of what modern day political correctionists tell you, this has always been fair in fair-minded society, and it is today's politically-correct zealots who have gone overboard in closing the doors of hospitals and medical schools to company reps, cutting off one of the most valued sources of new information that is out there. Good information is good information, and it is not tainted because the words issued past the lips of a pretty rep with a bag of doughnuts. But this system did have its abuses, and this is why YOU need to be in charge of honest and responsible assessments and choices about new products. It is unlikely that most me-too cephalosporins or beta-blockers will vary in efficacy or safety or side-effects. But if one prevails on better price or less frequent dosing, then those are meaningful differences. All aspects of total value must be incorporated into your evaluation of new products.

Then, in the 1980's, we had the bed wars. Support Systems International (SSi, now a part of Hill-Rom) and then Kinetic Concepts, Inc. (now KCI) had a knock-down drag-out over the hearts and minds and loyalties of hospitals and doctors buying and specifying pressure relief beds (there were and still are some smaller players in this field – apologies for not making specific mention of your names). Today, 20 – 30 years later, we take the concept of pressure relief so much for granted that it is easy to forget where we came from. When these companies offered fluidized sand beds, and then various types of dynamic airflow beds, these were bizarre products that few could be persuaded to start using, especially in view of the up front or rental expenses. (Sadly today, there are still hospitals, insurance plans, and their administrators who still do not understand why these expenses protect patients and save "millions" in the long run – but fortunately most do.) These beds were an example of just a very few visionary doctors working with companies to bring a concept to fruition. It was a combination of the clinical, technical, and financial principals, and then the doctors and nurses like you who prescribed the products, all having an equal role in the success of not just a company, not just a product, but of a whole product concept and concepts of care that have made modern hospitals a much safer place for sick people. But then something happened. Most hospitals and insurance companies eventually got the idea, and then the market changed. Instead of doctors prescribing specific products, hospitals or payors negotiated comprehensive service and supply contracts with one company or another. The companies might have duked it out behind the scenes with the administrators, but from the clinicians point of view, the bed wars abruptly ended. With little value to the companies to market directly to the doctors, the pizza-and-pencil promotions disappeared, but so too did the flow of good information and support and the direct ear-to-the-market of listening to the clinicians. And then it got worse. With other profitable products in their portfolios, these companies backed off on engineering and product development for the beds. Very recently we are starting to see a new generation of products coming out, but for the period of roughly 1995 – 2010, we have been using not only the same products, but some of the same filthy overused under-repaired individual units that we did 20 years ago. When the companies can no longer hear nor listen to the real clinicians – doctors, nurses, therapists – then real product development languishes. You the prescriber and clinician have to fight against the phony, the ersatz, the irrelevant, but likewise you have to fight to preserve the products that matter, or we risk losing our medical "civilization".



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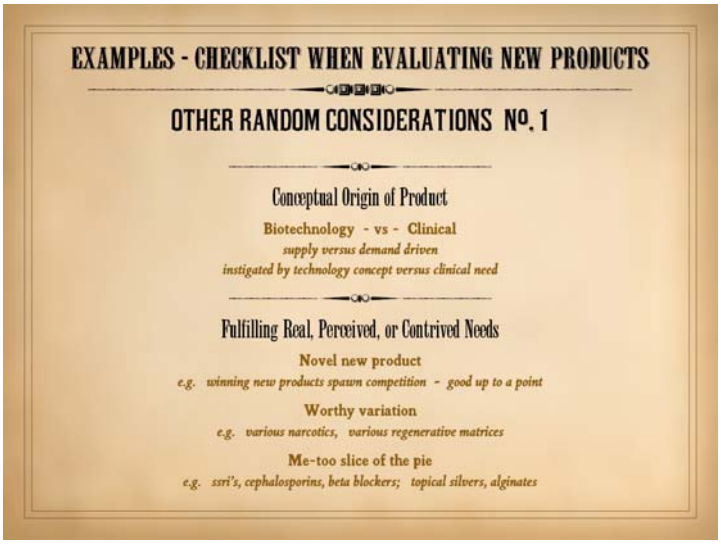
After you have gone through the above checklist for a new product, it is next time to add it all up and decide if the product is fundamentally worthwhile or not. And here to help you is Dr. Phelonius Cheatham, Professor of Snake Oil, from the practice of Doctors Dewey, Cheatham, and Howe, in Springfield. Take your initial impressions from the main checklist, and then apply them to Dr. Cheatham's Bogosity Matrix. This will allow you to ascertain if a product is Real or if it is Bogus.

The matrix is a simple 2x2 cross between two generalized parameters, Legitimacy versus Proof (each with a binary value). Is a product Legitimate? The answer is yes or no, some products are bogus, and some are real. Even if you do not know yet which way it goes, a product will be one or the other. Is there any Proof or confirmation of the product? It is either yes or no, the product either has some data, or it does not. Every product, old or new, will fit in one of the four cells. Every product should get certain attention and consideration from you which will vary depending on which cell a product occupies. Products may migrate to other cells as time, knowledge, and experience accumulate. The four states of the matrix are: **(1)** a product may be worthless and pointless and have no data to support it; **(2)** a product may be worthless and pointless but there will be some sort of data purporting to confirm its virtues; **(3)** a product may be meritorious but have little supporting evidence; **(4)** a product is meritorious and there is legitimate confirmation of this.

The matrix also has a sub-table of states that modify or augment your basic analysis: **(1)** a product might be made or marketed based on false pretenses and predicates, invalidating its use for certain applications, even if it has merit for other uses; **(2)** a bad product might be a consequence of bad design and engineering, even if it is conceptually sound and nominally fulfills a real need; **(3)** a product might get a false start or go in the wrong direction, but the sponsor can correct early missteps and get it into a new cell on the matrix; **(4)** a product introduced for one reason can prove to have other unforeseen uses or horizons, expanding the original utility of the item. These concepts will all be explained in further detail on slide 30.

The image is of John Greenleaf Whittier, 1807-1892, one of the Fireside Poets, and one of America's most notable historical men of letters. This engraving was published in 1892 to accompany announcements of his passing. His politics and philosophy were informed by his Quaker heritage, and his writings were always honored for their integrity and high morality. He was an ardent abolitionist and outspoken voice against slavery. His biography aside, I thought this portrait with its stern visage was perfect for the part of Dr. Phelonius Cheatham. At first I felt a bit guilty using the image of this principled man for such a low purpose, but then I realized, that as an alias with a stern theatrical demeanor, who better, as a genuine spokesman against moral corruption, to play the role of overseer of bogosity? Go read some of his poetry.



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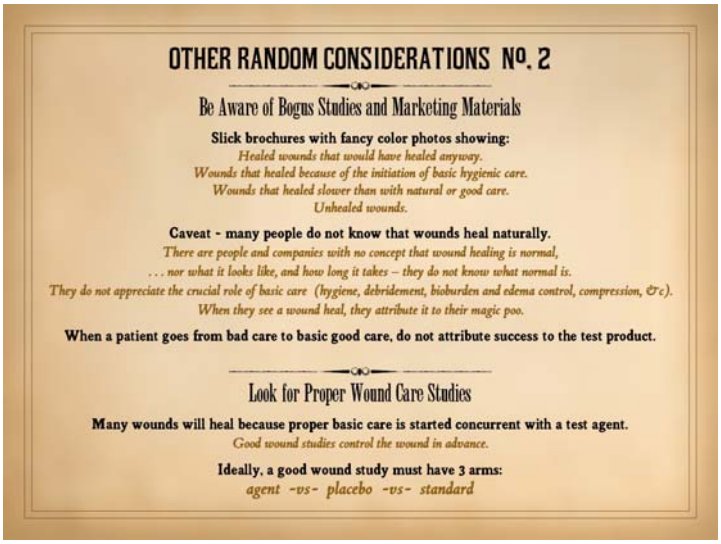
Before looking more closely at the bogosity matrix, this and the next slide mention a few random considerations, and re-emphasize some points already made. Remember, we are now discussing your evaluation of specific products.

What is the conceptual origin of product? Was the product demand driven, designed or instigated by a clinician looking to solve a tangible problem? Or, was it supply driven, instigated by a technologist-engineer-inventor who had a clever idea that may actually have little relevance to real clinical needs. There are of course many good, sometimes great game-changing products made by the non-clinicians. This is not a pejorative statement against non-clinical inventors. However, there are products that clearly have the imprimatur of a non-clinician, backed by a company looking to make a contrived need or market for a product that is already overly invested. Regardless how good and sincere the science and engineering are, if the product serves no clinical purpose then it is bogus. If your bogosity alarm says that there is no validity, do not be beguiled by the fact that a product simply got manufactured.

Does the product fulfill real, perceived, or contrived needs? When a novel new product solves a real problem, fulfills a real need, that is a boon to clinicians and their patients. As "imitation is the sincerest form of flattery", the real measure of such success is the me-too product. When a new product proves its value, other manufacturers will try to get a piece of the market. The competition can spur technical innovation and product improvement, and it can force lower prices and better service. After a while though, the value of competition declines as too many manufacturers offer too many variations on the same concept, confusing prescribers. Sometimes the variations and marketing claims on me-too products seem utterly frivolous and contrived, so beware bogosity on new products, but also when new players try to stake a claim in an already crowded market. However, if the new player is offering worthy variations, the new product might supplant your old choices, or give you an additional tool for specific situations.

For example, there are many narcotic painkillers in the pharmacopoeia that we prescribe every day. Do we need codeine, morphine, hydrocodone, oxycodone, and hydromorphone, and then all of the narcotic derivatives such as meperidine, pentazocine, fentanyl, etc? Yes, we do. Given the wide range of pain and its causes, the degrees of severity, comorbid pulmonary or neurological disorders, psychological and dependency profiles, receptor chemistry variations, and any number of factors, having a wide latitude for prescribing helps us keep our many patients relatively comfortable. When a new concept comes along like long-acting oral narcotics, it might at first seem like a minor variation, but then after a few years of use we realize how nicely it has altered our fundamental prescribing practices. In reconstructive surgery, we are seeing a similar event with the regenerative matrices (see slide 4). Some are structurally weak but malleable and flowable to fit complex geometries, some have an artificial epidermis that makes for excellent short term skin substitution, some are structurally strong for use in high-load musculoskeletal reconstruction, some are chemically cross-linked for long term stability, and some are not to permit relatively rapid resorption. Each manufacturer touts its own virtues and charms, but the reality is that these variations give the surgeon a range of tools needed to solve a variety of different problems. However, we are starting to see too many such products and companies (about a dozen in 2010), and soon enough the market will thin or consolidate as over-supply breeds confusion and diluted profits. The me-too mentality is also seen in wound care products. Just as for me-too pharmaceuticals, like cephalosporins, beta blockers, and ssri's, all kinds of wound care vendors want to sell a silver based product, an alginate, a skin care cream, and so on. While some variations of concept are worthwhile, there comes a point at which a silver is just a silver, an alginate is just an alginate, a topical steroid is just that, no more no less. The market for these products is huge enough that every vendor can get a tasty and fulfilling piece of the pie, but things do not work that way for more parochial products. Do not be beguiled by contrived claims of greater efficacy, and always consider price, convenience, service, and availability when specifying me-too variations.



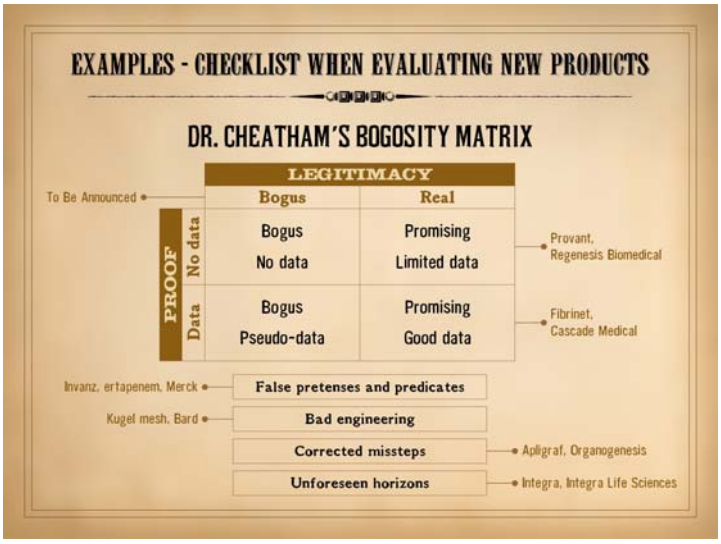
. . . random considerations continued.

Be aware of bogus studies and marketing materials. One of the problems with some products is that not only is the science and clinical development inherently faulty or bogus, but the product is touted with slick brochures with fancy color photos showing things that look good to the naive observer, but which are erroneous, misleading, and incorrect. Remember on slide 14 we talked about wounds which would heal anyway, and the trap of thinking a product is useful when all that was done was basic hygienic care to allow the wound to heal at its natural rate? It is common to see marketing materials that show: (1) healed wounds that would have healed anyway, (2) wounds that healed because of the initiation of basic hygienic care, (3) wounds that healed slower than with natural or good care, and (4) unhealed wounds that are claimed to be resolved.

Sadly, some people know so little about wounds, including some who develop, manufacture, and market wound care products, that these ironies are common. Common, as will be illustrated on slides below. The sad thing is that a potentially good product with stupid lame bogus marketing brochures risks being overlooked by knowledgeable practitioners. Sadder yet though, for medicine and our patients, but a bright spot for bogus vendors, is that even many wound care clinicians are sufficiently uneducated or gullible that such bogus claims can be attractive and effective. You, as the discriminating wound product evaluator and consumer, must not fall into the traps these companies have laid before you. The unfortunate and embarrassing reality for the Wound specialty as a whole is that many people simply do not know that wounds heal naturally. There are people and companies with no concept that wound healing is actually a normal event. Nor do they know what proper normal healing looks like day-by-day, nor how long the healthy normal process takes. They simply do not know what normal is, and they especially do not appreciate the crucial role of basic care to allow a wound to heal at its natural rate (hygiene, debridement, bioburden and edema control, compression, etc). Thus, when they see a wound heal, they attribute it to their magic poo in a medicinal box with a fancy full-color brochure – and they want you to believe the same . . . and too many do. The studies behind many on-the-market products did have genuinely positive outcomes, but that was attributable to standardizing the circumstances of the study so that patients were all suddenly getting basic good care. In a wound product study, when a patient goes from bad care to basic good care, then any further success cannot be attributed to the test product.

So, what should you, as the discriminating wound product evaluator and consumer, look for as a sign of a proper wound care study? Studies are detailed things, but two major items must be satisfied if the study is to be truly credible. **(1) Good wound studies must control the wound in advance of the test treatment.** In bogus studies, many wounds will heal, and the product will thus appear successful, because proper basic care is started concurrent with the test agent (or not at all). Good studies will have a "run-in" period. This is "phase 1" of all good wound care, a period of about 4 weeks, getting basic hygiene and wound control in place, taming the wild wound, and identifying those patients with easy wounds that will heal promptly with nothing other than basic hygiene and compression. This is no different than proper everyday clinical wound care, where the first phase, averaging about 4 weeks, is spent controlling the bad wound before then choosing discretionary options for stimulating or closing the wound. **(2) A good wound study should have 3 arms, agent -vs- placebo -vs- standard.** Granted, few studies do. The problem is that there is a well documented placebo effect in wound care and wound studies, and many wound product studies fail to standardize the conditions of the trial. When a study is designed that allows the clinician-investigator to do his "normal thing" in one half of the study, then his normal thing in the other half plus test agent, there will be no standardization and no meaningful comparison. The problem is that introducing the test agent will often radically altered all of the other "normal things", usually tightening up the details of basic competent care. Good wound studies, and especially those that are multi-center or multi-investigator, should have 3 groups. One group, standard, the study control, allows the clinicians and their clinics to follow their customary protocols and practices and decision trees. The second group, the placebo group, has a highly specified treatment protocol, including (as best as possible) a blind substitute for the real agent. The third group, the agent group, has the same

specified protocol plus the real test product (blinded as best as possible). If you could take many of the lesser or bogus products out there right now, and repeat their "pivotal trials" with this framework in place, many of them would have to abandon their claims. Many, it would turn out, would have poor results in the standard group (poor compared to accepted performance standards) and then appropriate but equal results in the placebo and agent groups. Even for good products, the placebo group should outperform the standard group, but then the agent group should do even better. The standard group would be less necessary in a well designed study conducted by experienced successful clinicians and sponsored by experienced reputable companies, but alas that is not the case for many new products. As the discriminating wound product evaluator and consumer, proper study design and analysis must be scrutinized by you to see if there is real merit or just bogus nonsense claims in the marketing materials shoved in your face. If the company reps or their higher-ups cannot explain nor justify how they did a study – which is common – bogus.



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Back to Dr. Cheatham's Bogosity Matrix. On the attribute of legitimacy, all products are either bogus or real. On the attribute of proof, all products either have data or not. Any product, real or proposed, preliminary or on the market, new or established, will fall into one of the four blocks on the matrix. Then, there are four ancillary analysis items that should help you think or rethink the position of an item in the matrix, especially when first impressions might be in doubt, or when prior art, knowledge, and truths conflict with proprietary claims.

Serious products that need regulatory approval must show some sort of evidence before authorization to market. This means that almost any regulated product already on the market, bogus or real, must be in the "with-data" boxes. When a bogus product is on the market, it means that its approval was based on bogus proof, meaning that the data is pseudo. But, these are the data and pseudo claims that will be hyped and sold to you. For most practitioners, trying to practice honest medicine with verified and approved products, these are the bogus products that you will generally encounter. It is incumbent on YOU, for the sake of YOUR patients, to be cognizant and wary of any claims and data until you can study, analyze, and verify their legitimacy.

There are bogus-no-data products, and they are generally of two types. (1) They can be early products, still conceptual, beta, or pre-market. If you are involved in early product design, testing, or consulting, you might run into these. (2) These can be consumer products that require little or no regulatory approval or oversight. You are likely to run into these if you yourself, or else your patients and acquaintances use herbal, folk, health-food and similar loosely regulated and tested remedies. Remember, many traditional materiae medica, "health store" remedies, and a zillion over-the-counter non-prescription remedies sold in pharmacies are legitimate, useful, and therapeutic. Being a more plebian remedy does not invalidate it, even if formal evidence is scant, but these channels are more permissive of illegitimate claims and patent medicine abuses. Sadly, the market for wound care products includes many such bogus-no-data items that make wound healing claims (i.e. proliferative, regenerative, and accelerative properties). Whether erroneous claims are made naively, innocently, and in good faith based on subtly bogus study design and data – or otherwise – it is up to YOU to be knowledgeable, discerning, discriminating, and critical about all products you prescribe, so that the "wool" is not pulled over your eyes.

The next few slides will profile some real products to illustrate the major domains on the Bogosity Matrix. These are all proprietary products, so there are a few rules to remember. First, I have no investment in any of them, nor any other relationship nor conflict of interest. Second, except for the badly engineered hernia product on slide 33, all products mentioned are legitimate in one way or another, most meritorious. I have opted not to get mean and show the dregs of incompetence among some of the truly bad products. The intent here is to show legitimate products, but demonstrate how they must be critiqued and understood. Third, much more information about these products can be accessed via the internet or from the company.

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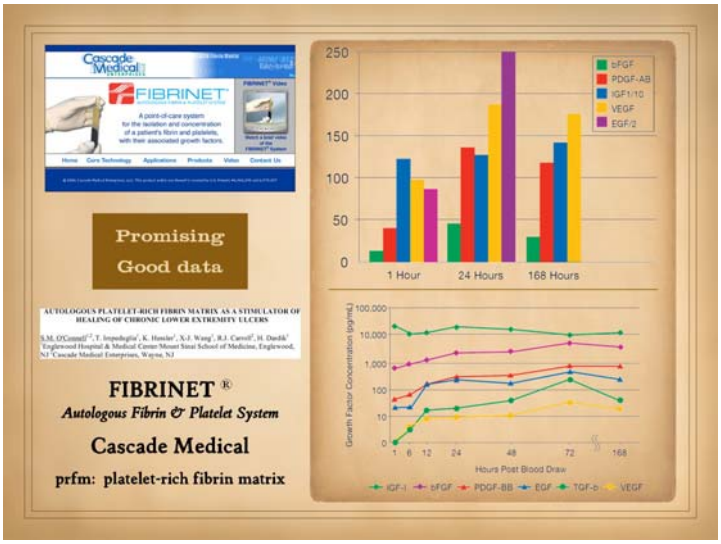
We will start these examples by looking at the domains on the right side of the matrix, products whose legitimacy is real. The first product reviewed, Provant by Regenesis, is in the category of **legitimate product with limited data**. It uses radiofrequency electromagnetic stimulation applied to the wound by antenna. The company is in Scottsdale, Arizona, my home town, so I have been through the company, seen the production line, seen the data, and most importantly, seen the cell cultures through the microscope. The system makes fibroblasts and other cells divide and proliferate. The photos illustrate published materials showing the effects of therapy on cell cultures and on gene expression. The in vitro biological effects are impressive, as I have seen with my own eyes. Does that necessarily translate into good clinical results? Not necessarily, but the potential is there. In actual practice, we have seen some patients have awesome good results, and some patients have no significant response.

Is it worthwhile? Yes. Does it have good science? Yes. Does it have good pre-clinical data? Yes. But does it have enough good clinical data to be persuasive to everyone, or to clarify when it will work and when not? Not yet from my point of view. Granted, there are clinical papers, but they are of limited experience, and from my point of view, not terribly persuasive. But remember, less than persuasive studies might reflect a lame product, but they might also reflect just a lame study on a good product. (Parenthetically, never forget that there are also way too many pseudo-persuasive studies on lame products.) Remember too, as discussed on slide 20, the "hearts-and-minds" liability that this product has being a physics based device. I believe in this product, but the reality of medical economy and manufacturing is that if not enough people use it, the enterprise fails, and the product never fully develops, then it goes away. So, some products deserve good faith acceptance and usage for a period of time, so the good items have a chance to become recognized and self-sustaining. Recently, this company switched from science-tech centric principals and management to business centric upper management, and perhaps now the clinical development and professional awareness that I believe this product needs will be heightened. Consider the one special value and virtue of this product: it covers large areas, so it is very practical and cost effective for large wounds In addition, there are no toxicities, it is extremely simple to use, totally safe, hygienic, pragmatic, useful for multiple wounds, no time or "dose" restrictions. As part of a strategy of sequential or integrated therapies, this should have a prominent role in the early phases of large wounds, when other modalities are limited by size, time, toxicity, and expense.



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The second example is also on the right side of the matrix, this time a **legitimate product with good data**. It is Fibrinet from Cascade Medical. It uses autologous platelets, prepared at bedside, and applied to wounds. It has been on the scene for only about 2-3 years. At first glance this might appear like any of the other half dozen or dozen autologous platelet products currently on the market. All of these products were developed to be hemostatics, to control bleeding, generally intended to be used in the operating room. Most of these products have also tried to extend their market into wound healing, the idea being that since platelets release the growth factors and initiate the events that lead to healing that they can be used as such. That concept might seem fair at first perusal, but there are problems with it. A dose of platelets might be made from 20 – 30cc of whole blood, the dose prepared in the operating room, then squirted on the wound just prior to closure. The fallacy is that during the course of surgery, far more than 30cc of blood thrombose in the wound, and platelets are being delivered, trapped, and discharged in high loads in any acute wound. So, how is such a product different than just normal bleeding and thrombosis due to the injury or surgery? The hemostatic effects of these products are useful and easy to measure and validate, but what about wound healing effects? I have tried these products – a sincere serious sustained effort during a one year period, on many dozens of cases – to see if a wound healing effect could be appreciated. It turns out that when these products are applied to acute wounds, any nominal wound healing effect washes out, gets buffered, is degraded, or is overwhelmed by other normal events in the acute wound. There is no appreciable difference in wound complication rates, nor have I seen any published data or even company brochures that validate such claims. These autologous platelet products have been engineered so that the platelets shoot all of their stuff at once, then it is over. They do what they were designed to do – stop bleeding. Contrast this to the original platelet releasate product, Procuren®. This too is made from an autologous blood donation, but it is processed so that one donation yields about 90 vials or doses of platelet material which can then be applied daily to a wound. Procuren was specifically engineered for wound healing therapy. Likewise, purified PDGF (becaplermin, Regranex®) was also designed to be used as a daily platelet substitute for wounds.

At face value, Fibrinet, aka prfm or "platelet rich fibrin matrix", would appear to be similar to the other hemostatic platelet products – draw the blood, spin it and process it right then and there, then apply it to the wound. What makes it unique is that the proprietary bedside processing

"chemistry", which includes precipitation of autologous fibrin, traps the platelets and allows them to stay "alive" and release their granules slowly, over a week or more. This slow sustained platelet release makes it a weak hemostatic agent but a good wound healing agent, and that is what it is intended for. The in vitro science and data are very strong, and there is supportive clinical data. The slide shows two graphs of various peptide growth factors found in platelet granules, specifically growth factors relevant to wound healing, angiogenesis, and fibroplasia. They show sustained release for 7 days, more than enough to have an effect on an acute trauma non-pathological wound, and long enough to permit weekly or biweekly dosing for chronic and pathological ulcers. The paper referenced is *"Autologous platelet-rich fibrin matrix as a stimulator of healing of chronic lower extremity ulcers"*. I have used this product too, and it does have a demonstrable beneficial effect on certain wounds, "kick-starting" impaired wounds that are not healing, or hastening closure of others that are making inadequate progress. This product thus fits in the category of stimulatory or accelerative wound healing products. The fact that the product is not yet widely marketed is due almost entirely to payment and reimbursement issues dictated by third party payors who generally are as equally confused about wound products as the government regulatory agencies. Remember, all good products have to start somewhere, and they depend on pioneer users and adopters. Whether you choose to try a new product or not should be predicated on whether it meets criteria of legitimacy. This product is conceptually legitimate, and the available data, basic and clinical, is good, putting this product in the most favorable quadrant of Dr. Cheatham's Bogosity Matrix.

If you are so inclined to test new products, to be the pioneer who tries new things, you will discover soon enough that to do so responsibly and to learn legitimate lessons means not getting overwhelmed or dividing your attention between too many new things at once. Regardless how busy your practice is, you still will have only so many patients, so many visits in a week. If you trial too many products at once, each will have a diluted experience of just a few patients, and you will never learn the nuances and sophistication that come from a robust experience. So, from the clutter and clatter of many new products, how do you decide which products are meritorious and worthy of trial? Which warrant your valuable time and attention to try to turn raw concept into tangible therapy? The conceptually legitimate product with good data, the right lower box of the bogosity matrix, will always be a worthy prospect.

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The next 4 slides illustrate the four ancillary analysis items below the matrix. Here is an example of **bad engineering** (the product pictured left). It is also an example of a **bogus product with data**. Remember, a product without any data cannot make its way to market, so even bogus products have some documentation. But if it is a bogus product, then its data must be bogus. "Bogus data" does not imply illicit, illegal, immoral, or deceptive. It simply means that something about it is wrong, erroneous, incongruent with proper methodology, misinterpreted, based on false pretenses and predicates, or tainted by a bandwagon or emperor's new clothes mentality of blind enthusiasm when reason and ration should have prevailed. Brought to market by the nice folks at Davol-Bard was the Kugel mesh, a hernia repair product whose introduction was trumpeted with the regalia accorded to rock stars and messiahs. Nowadays the only fanfare for the product is at the lowbrow websites of personal injury lawyers. (This is the one item here that is neither made nor marketed for wounds, but it is a good example of bad engineering, and since this subject is also an integral part of my own practice, experience, and consulting expertise, it was an easy obvious pick.)

This product was categorically brain dead from its inception. It should never have made it past any product review within the company. Its bogus engineering should have been axed before it made its way off of the napkin it was first drawn on. Its very design and then its clinical trials for abdominal wall reconstruction were done based on false intellectual and clinical-scientific pretenses by investigators with no expertise in musculoskeletal reconstruction. It came to market at a time when the long term problems of alloplastic materials for abdominal wall replacement were already quite evident. It was used mostly in patients where its use simply was not required (in lieu of a proper musculofascial reconstruction). Its approval was based on short term followups that the company and FDA should have known were too short for proper safety assessment. Among the many problems with this device, here is the "are you smarter than a fifth grader?" issue: it has a stiff rigid rim of plastic, but it is being inserted in a flexor surface that must bend. What happens when you bend a paperclip too many times? It breaks. And then those pokey broken ends of that rigid plastic thingamajiggy are going to poke and stab your chitlins inside your poor sick tummy. (You can read plenty more about this by searching on the relevant words.) Anybody with any basic knowledge of musculoskeletal reconstruction and the use of alloplastic implants could have told you how stupid this design was. What is shocking is that this product was developed, manufactured, and marketed by an extremely important reputable company that makes and sells many important safe effective products, a company with rich engineering resources that already makes other successful safe products for surgery and for various abdominal and musculoskeletal applications. Huh? What happened?

In this era, circa 2000-2005, it seems that many manufacturers had an idea about how to make hernia surgery better. Many went the way of developing biologics, the regenerative cadaveric matrices that allow new tissue to grow (see slides 4, 20, 28). On the right of this slide are some of the logos and names of companies and products in this biomatrix category (even Bard has products in this category). Biomatrices are not perfect either, but they are exceptionally safe, and they are highly effective when used properly by someone who understands musculoskeletal reconstruction. Alloplastic meshes still have a useful but narrow role, and we do need some basic cloths or meshes to support our surgery. However, there is little reason these days to continue developing complex or composite alloplastic devices for abdominal wall reconstruction, yet several companies continue to compete even against their own selves by developing new products along both lines, alloplastic and biologic. Nonetheless, several companies in this era came out with crazy complex alloplastic abdominal wall substitutes. They almost all suck. They

almost all cause needless severe complications and multiple redo operations as they are inserted, removed, then replaced with something else. As wonderful and important as Davol and Bard are (they are – no cynicism or sarcasm here), the Kugel mesh was an example of a company straying into a field outside of its traditional or core product lines and engineering expertise. It represents the kind of groupthink me-too mayhem and "madness of crowds" that makes you do things that on further reflection you know you shouldn't, a pied piper heralding the emperor's new attire, lemmings on the bandwagon that can make you abandon all sense and sweep you away on a ride to hell. It is an example of the concept "if you think you know the answer, you don't understand the problem", leading to mistakes that should have been obvious. You, the discriminating medical product evaluator and consumer have no control over how a company wastes its resources on bogus products. However, you can teach them a lesson and keep your patients safe by doing a thoughtful assessment, not jumping on the lemming's bandwagon, and not prescribing a bad or useless product just because it has been hyped or just because "everyone else" is using it.

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This slide illustrates the next of the ancillary analysis items, **corrected missteps** (with a bit of **false pretenses and predicates**). Apligraf®, made and managed by Organogenesis, is a living cell therapy which has become extremely important in chronic wound care and cure. In my practice and clinic, it is one of the most important products that we use, and we use it regularly. It is a wound stimulatory therapy, exerting a "pharmacological" effect on the wound to reverse chaotic dynamics and restore a proper wound healing trajectory to wounds which have been refractory and non-healing. We think of it as a pharmaceutical packaged in a living vehicle. The other comparable living biologic on the market for wounds is Dermagraft® made by Advanced Biohealing, Inc. It is also a great product that we use. This slide is an endorsement of the whole concept of living cell therapies for problem wounds, and it is an endorsement for both products, neither one over the other. I have used Apligraf as an example because I am much more familiar with its story, and its story is instructive.

When this product was developed, it was marketed as "skin-graft-in-a-box". The product had been developed by non-clinical biotech guys who get great credit for developing the technologies and creating a distributable product. They figured out how to take a skin specimen, extract pure fibroblasts and keratinocytes, re-engineer them into a living skin equivalent, then deliver the cultured skin in a petri dish for clinical application. They envisioned that zip-top-cereal-box skin grafts would obviate the need for autogenous skin grafts, thus emancipating every burn and trauma victim from the harsh realities of skin restoration. No. They might be forgiven their point of view, because as biotech guys, they developed this in mice, where immunogenic barriers to allotransplantation are not so strict. But people aren't mice. Those were the **false pretenses and predicates** behind the early marketing of this product, that because it worked in mice, they could now sell it as do-it-yourself skin grafts. No.

This concept runs headlong into the realities of allogeneic cross-individual tissue transplantation, something that we collectively in medicine had already been working on for over 200 years by the time this product appeared in the late 1990's. Consider the "Transplantheon" illustrated. Alexis Carrel won a Nobel Prize in 1912 for developing the technical arts of vascular surgery and organ transplantation. Karl Landsteiner won his Nobel Prize in 1930 for developing the knowledge and applications of the ABO blood types, opening the door to safe effective blood transfusion. Peter Medawar got his Nobel in 1960 for elucidating and applying the knowledge of leukocyte antigens (HLA), opening the door to allogeneic tissue and organ transplantation. Joseph Murray won the Prize in 1990 for being the first to actually transplant a whole major organ, the kidney. Thomas Starzl has not won a Nobel Prize, but he has won many prestigious awards and is considered the Dean of modern organ transplantation. And it all began with Giuseppe Baronio, who in 1803 (yes, eighteen03) published the first treatise on skin grafts. His work was important enough to wound healing and reconstructive surgery that the sheep he did his studies on are the logo of the Plastic Surgery Research Council. The science and arts of skin grafting and allogeneic transplantation are well developed, widely understood, and proof-in-the-pudding successful. With an historical and scientific pedigree that strong, it is rather pretentious and presumptuous of any company to come along and say that they have peel-and-press skin graft that can be "overnighted" by parcel post. But that is precisely the way that Apligraf was introduced to us.

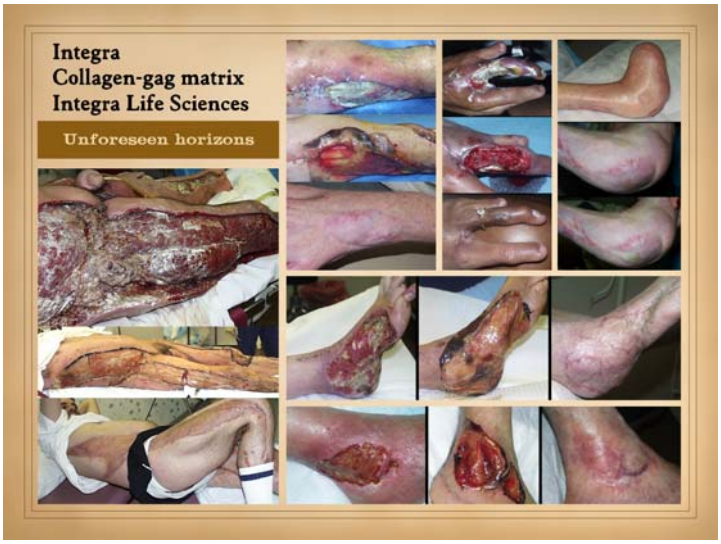
Personally, I found the concept of handy-dandy grafts completely erroneous and unbelievable. However, being aware of its development and approval to market, I begrudgingly tried it a few times, because when something is being that seriously hyped it deserves some sort of personal trial and evaluation. The product quickly degenerated on the wounds, and my first impression was "fly food". It was certainly not a skin graft, but then something else happened – problematic chronic and pathological wounds were appearing healthier and starting to heal. The grafts did not fuse to the host, but the living material applied to the host had a beneficial pharmacological effect on the wound. The effects were conceptually and tangibly comparable to the effects of therapeutic topical growth factors, which had been introduced to the market and available practice in the few years before Apligraf (as platelet releasates and recombinant PDGF). And then other doctors in our practice were having similar experiences – bad wounds were healing better as Apligraf could induce a wound module and ameliorate impaired wound dynamics. And then our nurses, doing the weekly dressing changes, started reporting their own independent observations of the same effects. And then other doctors in other centers starting observing and discussing the same things. Apligraf is not a skin graft. It is a wound stimulatory wound healing product, and it (along with Dermagraft) defined the concept of living cell therapeutics for wound healing.

As "skin-graft-in-a-box", this was a bogus product. As a wound stimulatory therapy, it is an item that we now find hard to live without in our wound care practices. How did it switch from lame to fame, from bogus to by golly? **Corrected missteps**. Users questioned, observed, analyzed, and the company listened. The company listened (not just Organogenesis, but much of the credit also goes to Novartis, the great pharmaceutical company that was managing and marketing the product in its early years). Not only did they listen, but they re-engineered their

basic science, clinical trials, and marketing and message to reflect the product's corrected identity as a wound healing biologic.

Here is another example. Remember Henry's Carbolic Salve back on slide 16? Killing germs with carbolic was never going to help Alphonso's acne. In fact, it risked making things worse by creating a caustic dermatitis – or – making things better! Here is the interesting twist on this story. We use phenol for "skin peels", a cosmetic technique that induces a superficial chemical "burn" that leaves the skin looking rejuvenated after it heals. As a face peeler, phenol went out of favor in the 1980's in favor of less toxic chemicals, but the concept is a standard part of modern cosmetic medical practices, including improvements for acne problems. Henry's Carbolic Salve might very well have actually done some legitimate good for Alphonso, but for reasons unrelated to the germ concepts and marketing claims that its developers honestly believed in. The pretenses and predicates were wrong, but there might have been a genuine therapeutic benefit. A company that corrects its missteps or false concepts can capitalize on that correction, for the benefit of its own bottom line while delivering a useful product that benefits its customers. These corrections all depend on user-prescribers and a good company keeping an open honest mind to realities and possibilities. For observant physicians trying to use carbolic products in the early 20th century, the utility of phenol for skin rejuvenation was recognized and incorporated into practice, regardless of any germ claims or prior conceptions.

The lesson is that new products must be tried, analyzed, and evaluated critically and objectively by YOU, the discriminating user of medical products. They must be looked at objectively, without bias, without preconception, and without paying too much heed to the marketing claims of the manufacturer and distributor. Whether a product is purely bogus or of stellar importance, it is up to you to discover and conclude so. Every inventor, manufacturer, and vendor makes positive claims – (have you ever heard a company claim "our product sucks, it's dangerous and doesn't do anything, but buy it anyway because our investors need to recoup") – so all such claims are meaningless until you yourself are satisfied of their veracity. A product that sounds good, or too good, might be bad. Or, as happened with Apligraf, a product that first sounds bogus might just prove its worth once you figure out what it is really good for. True bogus is bogus, but perceived bogus might have its virtues waiting to be discovered, and an intransigent company that will not listen to its users, customers, and beneficiaries may lose good opportunities. When a good company listens and reacts positively, the ultimate results can be a benefit to all – company, investors, doctors, and their patients.



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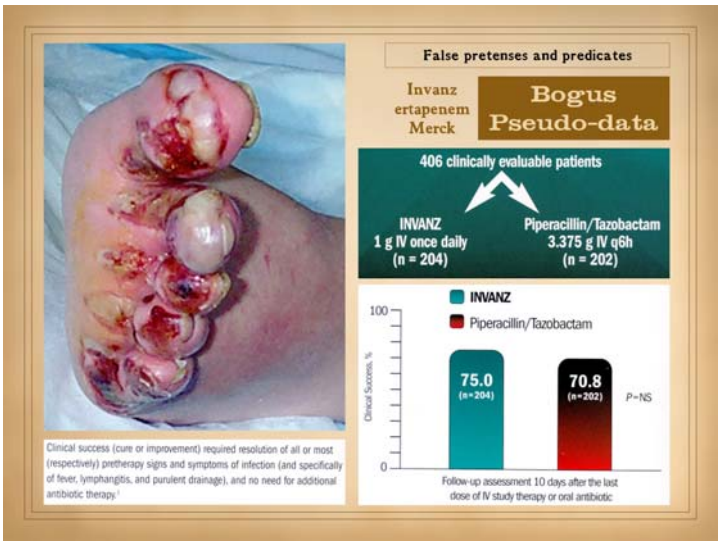
This slide illustrates the next of the ancillary analysis items, **unforeseen horizons**. There are many bogus and so-what products that claim to do everything but actually do nothing. There are also products that make extravagant claims but turn out to have a legitimate but limited scope of indications or uses. There are also the many products where promises and performance are proper and aligned. Then there are the occasional products that undersell themselves, like the one shown here, Integra artificial skin. In this case, the initial intent and first impressions of the product were positive and as expected, but the original principals had a rather narrow of view of its use – for burns only. However, it worked so well and was so versatile that a much wider range of uses and applications was discovered by surgeons, and indications exploded. It is a regenerative matrix, an implant that allows for in situ "tissue engineering" of embryonic new tissues, and it has found crucial roles in critical wound closure, acute repair, essential coverage, chronic wound closure, and functional reconstruction.

Much more information on this product can be found at the **arimedica.com** website and elsewhere. Illustrated are sample cases. **Left** is a patient with streptococcal necrotizing fasciitis whose life was saved and skin reconstructed with this product. Later reconstructive procedures for joint mobilization and contracture release were never needed, because this material creates an embryonic type of new dermis without scar. **Top left** is a patient with staphylococcal necrotizing fasciitis whose many wounds were closed, skin regenerated, and scars and contractures avoided by using this product. Shown is the dorsum of the hand and wrist where tendons were covered and closed without using the flaps that conventional plastic surgery principles call for. **Top center** is a hand with diabetic atherosclerosis and partial hand necrosis. The open flexor tendon and IP joint were closed and healed with no further risk to the patient or hand, and without needing conventional flaps which were not possible in these circumstances. **Top right** is a foot and ankle where pressure necrosis caused large heel and achilles ulcers in an old woman with marginal independent ambulatory ability. Simple closure of tendon and bone with Integra averted amputation and prolonged care, preserving her pre-morbid lifestyle, without flaps nor further jeopardy to the patient. **Center tier** is a foot and ankle following atherosclerotic events then operative revascularization. Open bones, joints, tendons, and ligaments were closed with the Integra. Just as for the preceding heel and achilles case, this elderly woman's lifestyle and function were preserved without amputation and without the risk of needing other donor sites. **Bottom tier** is a chronic ankle ulcer in a patient with a lupus-like auto-immune disorder, successfully closed with Integra when local flaps and other autogenous reconstruction would have been at risk for necrosis, lysis, dehiscence.

After this product was introduced to market in 1996, for burn closure, the wide ranging utility and value of this product was quickly perceived by many surgeons who applied it to many situations never conceived of by the original inventors and developers. That is why the ultimate role of any product is determined by YOU, the discriminating user, and not by the company, investors, marketers, or regulators. Of course, all the good insights and advice of users and customers mean nothing if the company does not listen and respond, but for this product and company, the "partnership" between company and surgeons was very healthy and productive.

On slide 11, in discussing regulatory agencies (paragraph #3), it was stated that ". . . good products [can] come to market with inane restrictions on use . . .", and this is a perfect example. For the physician experts and champions who believed so strongly in this product, there was a sense that

this was a singularly important and revolutionary product that needed wide awareness and acceptance. However, because the company originally perceived this as a burn care product, it applied to the FDA for a burn indication, and that is what was granted. Regardless how worthwhile it was for so many other things, the company was muzzled from making any marketing claims or talking directly to physicians about any indication other than burns. Communicating that message therefore depended on physician-to-physician channels. We would all agree that inter-professional communication and education is the way that things should be. However, getting that message out, which was considered so important by many of the early users, was hampered by the company being silenced on all but burn claims, and it took nearly ten years for these goofy and erroneous restrictions to be amended. For those who have had experience with this product, it is one of those few revolutionary products that appears in the course of a career that fundamentally changes the way we do things. It is hard to imagine practicing modern reconstructive surgery without this product (and other regenerative matrices). This means that those who perceive the value of the product for their own patients and practices also understand the need to promulgate the message, because if the market for the product does not grow and mature, then the product risks dying and disappearing. That is why YOU, as the discriminating wound product user, must also be enthusiastic about worthy new products, to help ensure that the full spectrum of uses and benefits is realized, to help teach it to others, and thereby to help assure the continuation of the product. It is the free market at its genuine and meaningful best, and it does not depend on "them" or "they" or "the company" or "the feds", but on YOU.



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This slide illustrates the last of the four ancillary analysis items, **false pretenses and predicates**. The product is Invanz, Merck's proprietary name for its preparation of ertapenem. Let us clarify up front that this is an important antibiotic, and it is coming to market via one of the oldest most venerable experienced pharmaceutical companies in the world. Many of the successes in our day-to-day care of sick people is thanks to this company and the products it makes. Undoubtedly Invanz has helped save the lives of many people with genuine infections and sepsis. It is a good product, indeed a very credible and important product, when used for what antibiotics are needed for – treating infections. However, it is not a good product for treating stinky armpits, nor for smelly flatus, nor for bad breath, dirty fingernails, nor belly button lint. It is not useful for wiping down your kitchen counters, nor for cleaning your toilet bowl, nor brushing your teeth. Its property of killing or inhibiting germs does not mean that it should be used for the quaint trifle of a pastime of killing germs with your chemical shotguns for mere sport nor for germ bigotry and germ fear-mongering. Yet much of the market and profits from antibiotic use are for treating non-infections. Wounds are wounds and infections are infections, and the two domains have a limited intersection. Yet when sophisticated problems like burns or wounds are cared for by inexperienced physicians dealing with problems outside their specialty, training, and education, then, the care always seems to turn to germ killing. Why? It is erroneous and detrimental to patients and the system for the many reasons discussed all along here. But it happens, and the companies who can profit from it do. Are the companies bad – is this a deliberate attempt to deceive doctors for corporate profit at the expense of added morbidity to patients and our health care economy? Or is it that the companies are themselves so naive about wounds that they make erroneous claims with bogus studies and marketing materials but which at least are made in good faith? I don't know. You will have to decide for yourself, case by case. Here is one of those cases.

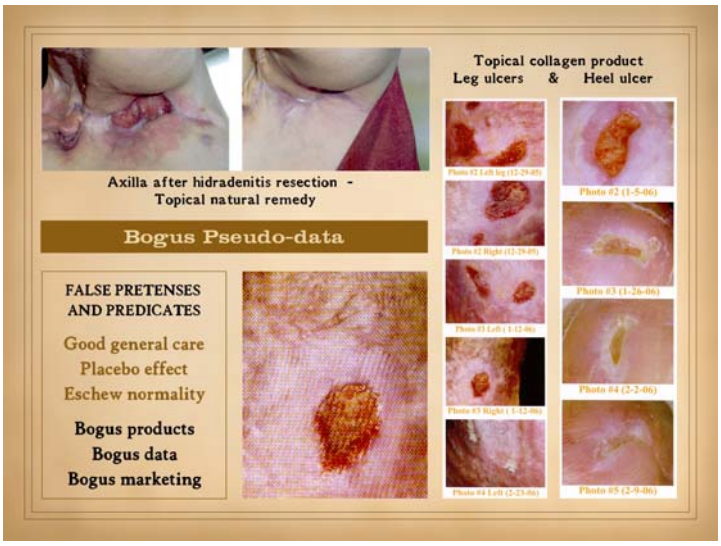
Pictured is a burned foot. There are exudates under the partial thickness blisters. The pattern of injury suggests a neuropathic foot – perhaps a diabetic standing barefoot on a hot sidewalk. Is this a trivial problem that is likely to resolve itself with minimum care? No. It is significant, and it warrants expert care. But any reputable burn or wound doctor will have this trouble-free within days and healed within several weeks. Is it infected? Probably not. Not having the benefit of directly examining the patient, one can only guess, but this is the appearance of any such foot several days or a week after the injury if it has been neglected or untreated. Erythema, mild edema, etc – all typical of the primary injury. What kind of care does it need? Some cleanup (minor debridement), some good topical care and hygiene, elevation and edema control, etc. Does it need antibiotics at all? No, not for the face value injury, not for what is shown in that picture. Topical antimicrobials – sure – but systemic antibiotics – no. To the extent that there is "pus" under the blisters, that goes away with simple debridement and proper topical care. Even if there is some infectious "cellulitis" component to this, does it need intravenous antibiotics with one of the newest most expensive drugs there is? The picture caption claims that the patient had fever and lymphangiitis. That claim would seem exaggerated given the picture shown – all the more reason that if it was true, we should be shown the evidence so we can understand the atypical advanced nature of the problem. Absent any meaningful, honest, forthright information to let us judge for ourselves, these marketing materials remain unprofessional, either deceptive or just dumb, and thus bogus. Proprietary marketing materials notwithstanding, this wound needs the basics of care just described, along with any prudent choice of safe, inexpensive, easy-to-manage oral antibiotic to cover normal skin and foot flora – e.g. tetracycline, sulfa, clindamycin, erythromycin, etc. If the patient is also vasculopathic with arterial insufficiency, that is an added risk that could justify more aggressive antibiotic therapy, such as cheap, effective, safe (when used properly) vancomycin, and even then just for the few days needed to allow the other components of care to correct the risks and acute conditions. I treat problems like this day in and day out. So do my colleagues in my own practice. So do my wound care brethren in legitimate wound practices around the world. My patients get better. So do theirs, by doing the basics. I would never think that this requires a hospital admission, nor would I ever contemplate giving intravenous antibiotics for this situation, especially the newest most expensive drug.

Note the other graphs in their materials. They show that compared to piperacillin-tazobactam, there is no difference in therapy, but Invanz is implied to be cheaper and easier to use. Part of this is categorically true – that once-a-day intravenous administration is better than four-times-a-day. Who can argue with that? Of course, one also has to know how much the drugs per se cost, per dose. While the cost of Invanz is not

reprehensibly high, there have been other antibiotics within the past decade where the cost of the drug per dose way offset and overwhelmed the costs of IV administration. But notice the two bogosity trail markers here, the bold numbers and the graph axes. First, the big numbers – 75.0 versus 70.8, green Invanz for go, red pip-tazo for stop. The way the numbers are shown, they are meant to imply a difference. Think about it for a moment, and you realize that there cannot be any statistical significance in those numbers – and the fine print byline confirms "p = NS". From a technical statistical and regulatory point of view, that was one of the purposes of this study, to show that Invanz was no worse than pip-tazo, implying that if it is no worse than it is just as good, and thus even better if it has some other virtue, such as less expense or less frequent dosing. And that is the honest message here – that there is no difference between the two drugs, but Invanz need be given only once a day – and that is a genuine virtue and good message. But the message that the company really wants to convey to the consumer-prescriber, via these fancy 4-color marketing materials with pseudo-science and pseudo-doctor speak, is really meant to sell you by a more visceral subliminal persuasion. You may not remember much from this brochure, but odds are you will recall "Invanz, 75% is better than 70%". Remember, the guys in their marketing departments and ad agencies have four-year college degrees where they learned to do just this kind of amoral stuff. But even that is not the ultimate bogosity . . .

The ultimate gut-wrencher for Dr. Cheatham are the axis labels on the graph: "Clinical Success, %" – versus – ""Follow-up assessment 10 days after the last dose of IV study therapy or oral antibiotic". First, the graphics show IV therapy versus IV therapy, so where did "oral antibiotic" come from? Did I miss something, or did they, or are they trying to confuse me? More importantly – and this is what all decent wound doctors know, and what companies and people who do these bogus studies do not know – is that a 70 or 75% success rate treating this problem is far too low, so low that it should be an utter embarrassment and cause for close scrutiny of professional performance and quality control. A success rate of only 75% for this problem is not standard of care and is not acceptable. Legitimate wound practice has certain benchmarks of care and outcomes, and nobody in the legitimate practice of wounds would accept such low numbers. The problem with so many studies like this, is that they are done by people who kill germs for a living, but who do not take care of wounds. They are done with protocols that define the use of the study agent, but the patients rarely get any of the proper wound care modalities that they need. As a wound study, investigations like the one shown are almost invariably designed improperly, designed to show what the company wants shown, and not designed to show the legitimate wound care effects of the product. It would be as though a company is looking at the effects of a broncho-dilator, and that everyone with a wheeze is randomized to our drug versus their drug. The cause of the wheeze is irrelevant – generic asthma, seasonal allergies, the patient just had a myocardial infarction or his mitral valve prosthesis just went kaflooey. No matter, the patient gets the inhaler – just the inhaler – no steroids, no diuretics, no antihypertensives, no inotropes, no angioplasty, no surgery, no respiratory therapies – just the simple inhaler. And then, 10 days later you assess the lousy outcomes and conclude that your drug led to a 35% success rate versus the other drug which had just 30%, p = NS. Welcome to the world of "wound studies" and the bogus ancillaries, such as antibiotic studies to treat "skin problems". The patient shown here had a wound, he got treated for infection, and the overall outcomes are substandard because it is all a classic "apples and oranges" confusion. Is the company being deliberately deceptive or just dumb? You decide. Either way, the patient(s) shown should have had far better than 75% good outcomes if they were being treated properly for the correct diagnosis by physicians who are experts or even just knowledgeable about the problem.

Are these marketing claims made for the benefit of you and your patient, or for the company to sell you something that was expensive to develop and is expected to garner Billions of dollars in profit? Did the company know that this does not require such expensive aggressive treatment, but they don't care? Or did they really believe all of this, because they are not experts on wounds, and they have wounds and infections confused? Are they confused about the two naively and stupidly, but nonetheless honestly, or have these companies undertaken a vast social engineering project to deliberately confuse these issues in the minds of inexpert physicians? (It's the Willie Sutton Rule - that's where the money is.) I don't know. You decide. To reiterate – ertapenem is an important pharmaceutical. It earns its revenues for the company when it is used for genuine infections. But implying that the picture shown is an infection, and that it needs antibiotics at all, and then to treat it with intravenous therapy, and then to imply that the great outcomes were due to this, especially when there were no wound controls and no third arm and no run-in period in the study – all of this is ultra pure bogosity. The saddest thing is that in the current meltdown of our medical education system, young doctors and young minds are not getting their requisite learning and mind-training from their schools, their professors, their experienced attendings. They are getting fud-based pseudo-information from marketing claims such as this from companies who have boards of directors that demand billions in profits at the expense of all else. Until Wounds becomes a robust substantiated specialty with a normalized curriculum and non-trivialized representation in universities, then bogus claims and marketing materials, such as confusing normal wounds and injuries with infection, and thereby using wrong therapeutics, will hold greater sway over the (non)-intellectual development of young doctors and nurses. This case example is entirely based on false pretenses and predicates. All of the logic, all of the syllogisms, all of the conclusions of this study and the marketing materials shoved in your face, all are based on the erroneous predicate that this simple injury was an infection. Furthermore, it is all discolored and fogged by the erroneous-at-best and immoral-unethical-at-worst pretense that any skin or wound problem is an infection, and that uneducated physicians working outside their specialty can be duped into spending money for one of the most potent fud weapons that the for-profit fud mongers have – playing the "infection card".



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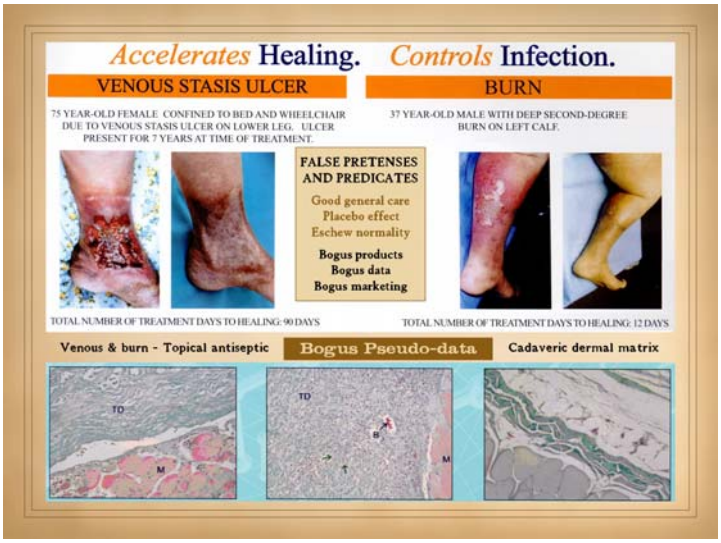
On slide 30 I explained that most of the products shown here were selected because they are not bad but must be critiqued, and you must learn to see through the smoke and appreciate the wheat versus the chaff. The four products shown on this and the next slide are all of that sort. These four products are all potentially meritorious in one way or another, and they all deserve some nominal respect and a chance to get going in the marketplace. The problems are that, regardless whether the products work or not, either the development and investigations behind the products or else the marketing materials are all bogus – lame, ill-conceived, inexpert, poorly executed, illogical and non-sequitur, predicated on false pretenses and lacking robust (or any) knowledge of wounds, and dumbed down with advertising materials that epitomize the "if you can't dazzle them then baffle them" philosophy of persuasive marketing. One would hope that potentially good new products would have the benefit of honest expert development, because everyone then benefits.

The first product is **upper left** on this slide – the armpit. The product is for a honey based dressing. Remember what the first part of this talk was about, a precis of medicinal history, in which we extolled the potential value of the vulnerary remedies in the historical materiae medica. Any modern scientist or clinician looking to develop a classical remedy for wounds could hardly do better than to focus on honey. Honey has a long tasty tradition of being good for wounds. It should be noted though that when you read original sources about the virtues of these remedies, that honey's wound effects tend to be similar to the balsamic resins (myrrh, benzoin, peruvian) – emollient, antiseptic, and anti-inflammatory – all important properties to be sure, and in fact a rather sweet and acceptable way to provide basic care for wounds. However, just like Paré and his use of rose oil and turpentine, the effects are probably to restore the wound to an environment that allows wound healing to progress at its own optimized rate, not however to accelerate wound healing beyond its native kinetics – unlike other vulneraries such as symphytum, achillea, prunella, and arnica in which classic observations and use imply a genuine stimulatory effect. Either way, honey has an acknowledged place on wounds, so we can readily conclude that what is shown here is a legitimate potential product, but what has the company done to prove it or improve it? Have they done right by the industrious little bees who make it, enlightening us with a pathway to the most effective use of this remedy for the sake of getting patients better faster? Regardless whether the product is good, great, or indifferent, the marketing materials are nothing but patent medicine hype – trite, trivial, cliched, bogus. And that is too bad because potential real therapies deserve a chance for genuinely good investigation and development. Concerning the case shown, the marketing brochure states *"44-year-old patient with hidradenitis suppurativa for 7 years; Wound excision and use of a variety of dressing types were unsuccessful; The wound healed in 5 months after application of OUR PRODUCT dressing*". The misleading problems here are several. The wound excision was not unsuccessful – it was completely successful in removing the primary disease, and now she no longer has hidradenitis, just a residual wound without the primary pathology. A transverse axillary wound (after hidradenitis excision or for any other reason other than radiation) is expected to heal rather quickly. If it does not, then there are just a few reasons why – persistent primary pathology, versus some undiagnosed wound pathology, versus biomechanical impairments of contraction due to scar and motion, versus inept injurious care. Absent any other history, no further inferences can be made. If we assume that any of these causes were present, and then the patient switched over to good basic care using the honey product, then we would expect to finally see a good outcome. If the excised wound was open and unhealed for 7 years, then thick scar will impede contraction, and a 5 month interval to closure is not surprising. If the disease was present 7 years, but the excised wound is recent, then only 5 weeks should have been needed to get the wound closed with any reasonable care. The point is that after so many years of frustration, that whoever inherited this patient and took care of her did a great job and the wound healed. Kudos – whether by design or by the placebo effect (the placebo effect in wound care happens when the patient or care provider, bored and disengaged from the process, gets beguiled by an interesting new product enough to get actively involved in the required daily care). Everyone in the wound business can appreciate how nice this result is and understand that 5 months to a good result is "within bounds". The question is, did bee goo save the day, or just the effects of non-specific but competent care? While this is a genuinely nice result, it probably just reflects basic competencies, and nothing at all extraordinary about the dressing per se. If you are naive about wounds, if you do not know what normal wound physiology is all about, then it is easy to imply, via bogus marketing materials, that the wound would never have healed but for the magic medicine. The disappointment here is that the magic potion did not accelerate the wound such that it closed in just 5 weeks – that would have been a genuinely notable result. Alternately, perhaps the wound would not have closed in even another 5 years were it not for the honey – we can never know. But the actual time frame involved can be appreciated by an experienced wound observer to probably represent the effects of competent basic care, not a pharmacological effect of the honey. How could you ever know the difference? By doing a randomized controlled clinical trial – one that is done properly and done explicitly as good wound RCT's should be done – and there just aren't very many of them. Will the honey product ever have a compelling study behind it? Probably not. RCT's are expensive. Making markets of new products is difficult. Regulatory requirements can overshadow all else, and when a safe natural remedy like honey can come to market easily without too much scrutiny, no CEO is going to want to spend millions that aren't a regulatory requirement just to prove a point, especially when the bogus marketing materials that they print will be sufficiently persuasive to enough people to make their market.

The other photos on this slide are case studies sponsored by the manufacturer of another product, a "hydrolyzed collagen powder". Collagen as a putative topical wound healing agent has made its way into many products over many years. The romance of collagen is anchored in the sciences of the 1950's, and whether or not it is of any meaningful value as a topical vulnerary is highly debatable. Nonetheless, even today, companies keep trying to get a me-too piece of the collagen pie, when their productive attention should be turned to other chemicals of demonstrable significance (see slide 22). Two case studies are shown here. The **right column** shows *"a 71 year old diabetic, hypertensive patient with a five month duration, non-healing post surgical wound of the left foot*". The photos show the wound over an interval of 35 days of treatment with this collagen product. The wound is not yet 100% healed, but the progress is excellent. The wound is clean, free of inflammation and injury

– obviously very well cared for by somebody with some knowledge and competencies to do this. The **center column** is "*a 75 year old obese patient with peripheral vascular disease and chronic slow healing leg ulcers, partial thickness wounds of bilateral lower legs*". The pictures cover an interval of 56 days with all demonstrated wounds healed. Once again, these same authors provided excellent care and got the wounds healed in an admirably short time. Look closely at the enlarged view (**bottom**). Do you see the imprint of the gauze pads? This leg was being wrapped and compressed and had all of the things that are crucially important to good outcomes. These ancillary activities, like compression and edema control, are the quintessentially crucial activities that must be done if any wound is too heal quickly. These are the things that qualified wound people do every day but which unqualified providers know nothing about, and which are trivialized by reviewers at regulatory agencies and editorial boards. So, are the good outcomes here attributable to the good nurses who took care of these patients, or to the magic collagen sprinkles? Herein is the fundamental problem with "studies" like this: you just don't know. These wounds had good care and they healed properly. The time frame is "quick", but not extraordinarily so. The short intervals could not have happened without excellent care, and many patients with comparable wounds and care would have had similar good outcomes without magic sprinkles. Yet our benchmarks for good care would have allowed these patients twice as long to heal, so perhaps the collagen powder did make a difference. The authors attribute the good results to the powder without giving themselves enough credit, and that is a perfect example of the placebo effect and "emperor's new clothes syndrome" in this business, getting so beguiled by what's new that you lose sight of what really matters. The problem is that "studies" and case reports and marketing materials like this do nothing to help discriminate good care from pharmacological effects. Without a properly done RCT, you cannot answer this question. Furthermore, the brochure states "the hydrolyzed collagen powder stimulated fibroblastic activity within one week . . . " Whether that is true or not is irrelevant, because it is just a trite inference made without any histology or other micro-assay, stated improperly without regard for the known biology of these systems. The patients got better quickly. Their nurses did a great job. Perhaps the collagen powder made a bit of a difference. That is all you can say without a formal investigation.

Both of the products shown on this slide are nominally legitimate, and both are potentially useful with theoretical positive pharmacological effects on the wound. Yet the documentary information that would make that case is non-existent, and the marketing materials are naive and lame. The problems is that lame materials like this can persuade those with little or no knowledge of the subject. If a potentially good therapy has only bogus materials to support it, then what happens when illegitimate products shovel the same nonsense in front of you? Whether or not you prescribe something is your choice, but it is your knowledge, good faith, and common sense that are the last line of defense against bogosity and potential medical or economic harm to the patient.



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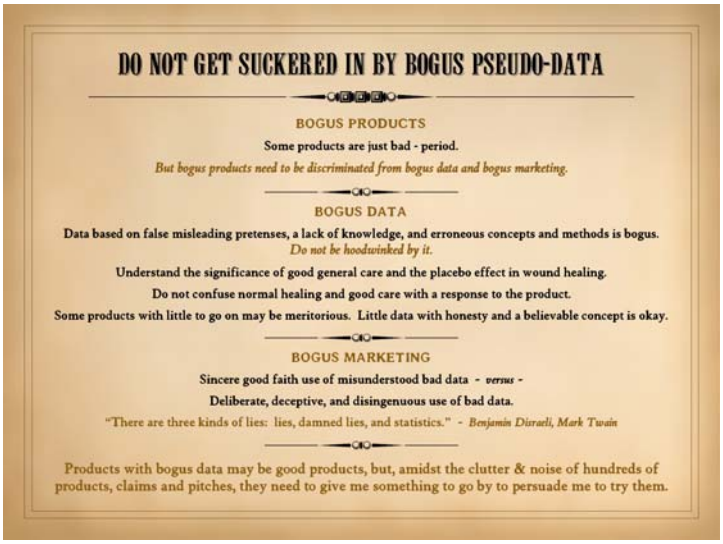
This slide will focus on the bogosity in the brochures that are waved in front of you in the competitive marketplace of the trade show exhibition hall. Those brochures are some of THEIR the companies main armaments to win your hearts and minds. These brochures are designed to be eye candy, meant to tempt you even though the products they hawk may spoil your dinner for good care, and your mom keeps telling you it's no good for you. The **bottom panel** shows some photomicrographs of a biologic, a regenerative matrix made from human dermis. These products are used in surgery for a variety of reconstructive purposes. Their value is affirmed, and many companies offer competing products from human, bovine, ovine, porcine, and equine sources. These products also have a useful role in treating certain chronic wounds, so not surprisingly these products are represented at the wound trade shows. The product is not bogus. It's applications are not bogus. The bogosity here is in the sales brochure – it is meant to dazzle you with pseudo science, little teases of technical information that give an aura of legitimacy, but which are so scant on meaningful information that knowledgeable observers will find nothing of substance. I chose this example because of the histological pictures. Good histology should be one of the most valuable forms of information to be shown for any wound product. This is a good example of worthless histology. Being technical in nature, the mere fact that a photomicrograph is included on the brochure gives a mien of authority to the company-product-brochure. But, this histology is badly presented, and in fact it may hide the real story that discriminating users might want to know. **Left** is a picture of bare matrix sitting on top of muscle "explanted at day 1" (Masson's trichrome). There is no mention of how the study was done, what kind of animal was used for the implants, where the material was implanted, nor any explanation of what you are looking at. Do you know how to interpret this? The brochure gives absolutely NO other information other than what is already given – trichrome, explanted at 1 day – that's it. There is a footnote reference to a bibliographic entry that concludes with "unpublished data". Unpublished data is by definition not a bibliographical entity at all, so a formal bibliographical citation is nothing more than smoke and mirrors bafflement meant to give an aura of legitimacy. Either way, if unpublished, how do I find the article to find out what species was used or other details of the study? **Middle** is a picture "explanted at day 7". The general intent of the first picture was to show that at day 1, there is no cellular ingrowth into the implant. At 7 days, the matrix is full of cells. Or so they say. Can you really see what is going on in that low power under-resolved 5cm picture? Histology pictures can surely seem impressive, but you must not be naive and be awed simply by the presence of the picture. You must be discriminating and analyze the information on that picture. So, let us "read between the lines". There is a general sense that cellular material has filled the matrix. For those of us who have spent years studying these products and scrutinizing hundreds of histology specimens, there is something not quite right here. One week to filling of the matrix is wrong. Histogenesis will go faster in smaller species, so if this was a mouse or a rat, that is partially understandable. But the arrows center-bottom are labeled as neutrophils. (The arrow to the red thing is labeled "blood vessel", but how would I really know with such a poorly resolved image?) The problem is that neutrophils should not be there. Period. But if they are there, acute inflammation is one good reason why the matrix would have filled quickly, just with the wrong stuff. The regenerative matrices, used properly, suppress inflammation and wound healing and trigger an embryonic type of histogenesis (tissue formation). Neutrophils have no business being there, unless the implant was processed and handled improperly and got infected, or unless the

implant has triggered an immunogenic response. The poorly resolved view that they give us suggests that there is no suppuration, so we can give them credit for a clean product and clean surgery, no infection. But the immune response question is key. Cross-species studies with these matrices are prone to these events, and if the implant becomes inflamed, then it heals with scar, and the whole premise behind regenerative matrices is invalidated on these particular studies. The manufacturers who make xenogeneic implants for human use understand this full well, and they all claim their own proprietary process for removing collagen epitopes or otherwise reducing immunogenicity. Since the product illustrated is from human sources for human recipients, reducing immunogenicity need not be done, but doing cross-species studies like this does little to inform anyone about the virtues, uses, and pitfalls of the product. But those histology pictures sure do look important, don't they? **Right** is a picture "explanted at week 8". There are no labels or other explanation. I am guessing that the green band across the middle is meant to be the healed or regenerated matrix. I am guessing that the clear areas above are the panniculus adiposus under the skin. Nothing is labeled. That green band across the middle could just as easily be the native endogenous muscular fascia that ordinarily belongs there between muscle and adipose. Notice how the green band seems quite thin compared to the matrix thickness on the other images? Are they deluding themselves – and you – by claiming that this is the regenerated matrix? How is anyone going to know on a tiny low power low-res image like this? But it's histology by gosh, it's gotta count for something! The legitimacy of regenerative matrices is not in dispute. This is a credible product from a credible company. But as soon as an ad agency is put in control of professional communications, all you get is bogus brochures that have one and only one intent – to sell you something. So, they can be completely disrespectful of your knowledge, education, and intellect, yet still be persuasive, and they can be equally persuasive for bad products as for good products, and all the more so when the intent is to baffle you with stuff that oftentimes neither the company people nor the ad people nor the target audience has any real expertise with. So, don't be taken in by tricolor trichrome pictures. Analyze, learn, listen, question, be skeptical until THEY can provide you with intelligent information, and never let bogus brochures persuade you with pseudo-scientific drivel of no real intelligence.

The **top panel** shows advertising materials for a prescription wound product. This topical ointment might be useful and legitimate, maybe not, and it is certainly not harmful. The bogosity is in that even if it does do something useful, that claim is never proven or supported, and the marketing materials are a grotesquely bizarre mishmash of error, irrelevance, and misdirection, a copywriting sleight of hand meant to imply magical effects and results. The ointment contains three chemicals derived ultimately from natural sources, and which have a long safe track record in topical skin care products – benzoic acid, salicylic acid, and oak bark extract. Shown **left** is a venous stasis ulcer of 7 years duration, healed in 90 days with the advertised product. Is 90 days (13 weeks) to closure a credible performance within or exceeding customary benchmarks of good wound care? Yes, it certainly is. Is it a magical performance? No. Was the care accompanied by good hygiene, good compression and edema control, periodic debridement and maintenance, et cetera? Not stated, but we all know that there is no magic goo that works well without these other modalities in effect. Did the goo work, or just the good care? Can't say. The other picture **right** shows "deep second-degree burn", healed in 12 days. Is 12 days to being healed something for the caretakers to proud of? Yes, it sure is. But did the magic goo help to accelerate healing, or is it just that competent care in any form would have allowed this to heal at its natural rate? As a burn surgeon, I disagree that the injury shown was "deep second degree". It is a superficial partial thickness injury that might well heal in 12 days with tip top care. Of course, many patients get care that is not so good, and this patient could have done far worse. And even with good care, this could have taken several weeks to closure, so the result is noteworthy, but the case is not proven that the ointment had pharmacological accelerative effects on the wound.

There is more histrionics and melodrama in this advertising brochure than there is substantive information that knowledgeable practitioners and prescribers would want to know. The brochure presents several other cases in which isolated wounds are shown with inaccurate diagnoses and no mention of any of the other required ancillary care. All had benchmark times to healing reflecting good general care, and some of the times are good enough to wonder about possible pharmacological effects. But the brochure has no meaningful technical information. There is no discussion of pharmacological properties or presumed mechanisms of action. The brochure is plastered with tables of bacterial susceptibilities, with the implication that the product kills germs, ipso facto it heals wounds. The brochure flashes consumer marketing graphics in your face claiming "stimulates re-epithelialization, debrides, inhibits microbials, moisturizes, affects vasodilation". No agent does all of those things. Even if the combination product did have all of those effects, there should be some technical discussion to document or explain these effects, and some tables or graphs of data or else photomicrographs or something meaningful to confirm these effects. Of all the lousy brochures I have seen, this one is uber-remarkable for the complete triumph of marketing over science, data, and doctoring. And yet, the product might actually be good. Once again, we have here a product derived from natural sources that has promise as a legitimate vulnerary. Legitimate investigations should be done, laboratory and clinical. But that will never happen. Why? This is not a scientific pharma product coming from an established company with proper resources, nor is it a novel pharmaceutical coming out of a research lab in which clear cause-and-effect on the wound has been demonstrated. This is a compounding product. Stock items, with putative wound care and-or wound healing properties, were pulled from the shelf and mixed in a goo. The goal is to get this product to market and make money. It is the type of product more properly suitable for a health food store. The marketing materials are consumer oriented and care little about the scientific basis for the product. The brochure was put together by the marketeers, and there is marketing-speak all over this thing. The goal is to persuade and sell, not by letting the product speak for itself, but baffling you with bravado and hype because the science behind this product has no voice of its own. This is the patent medicine trade rearing its ugly head, and shame on any doctor who falls for it. Except that this particular product has some legitimate potential merit – it might actually be a good product – but the company did not show you credible evidence, only the patent medicine hype, the bogosity. Recall that I opted not to get mean by showing the completely dishonest products but they all have similar kinds of brochures – all hype but no legitimacy, all form but no substance, all meant to persuade and sell at any cost regardless how worthless the product is. There are plenty of such products that make their way to market for shorter or longer periods of time. The ultimate problem is that if this kind of salesmanship can persuade you to prescribe this stuff, then this kind of salesmanship can persuade you to prescribe anything. If you are going to use this or any other product with bogus brochures because you perceive the possibility that the product itself might have some genuine usefulness, then by all means do it – that is how progress is made. But do not use it blindly, stupefied into obeisance by the pied piper of a company tooting a magic flute made of bogus brochures. You must remain in charge of the analysis and choices, and you should insist on better information. And if you do choose to try such products, do it thoroughly, do it wisely, record legitimate information and results, then good or bad share that information with your colleagues so that the cream can rise to the top and the dregs can sink into oblivion.



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Bogosity comes in many forms. An item and everything about it may be worthless – a **bogus product**. Regardless of its intrinsic value, good or bad, its proof may be faulty – **bogus data**. Then regardless of its value and the evidence behind it, it might by promoted by illegitimate claims or by false pitches – **bogus marketing**. The final message in this section on the Bogosity Matrix, with its case studies, is "do not get suckered in by bogus pseudo-data". Do not be hustled by illogical and falsely substantiated claims, nor let your patients and their payors be raped in the wallet with false expectations.

Some products are just bad - period. You want to recognize and avoid them. Remember, if they are on the market, they got there by pseudo-legitimate data, so you need to be alert to bamboozlement and make your own discriminating analyses and judgments. However, on this slide, I also want to emphasize the products that are potentially meritorious, but which have problems with their proof and their marketing, so that even when you sense some bogosity, you do not indiscriminately toss the whole product. Bogus products need to be discriminated from bogus data and bogus marketing.

Bogus data is that which is based on false misleading pretenses, a lack of knowledge, and erroneous technical concepts and investigative methods. Do not be hoodwinked by it. In any in vivo or clinical study of wound healing, especially the clinical studies, always be alert to the placebo effect and the improved outcomes that result just be doing an investigative study. Very few wound products have done a three-arm study, as they properly should. For any study, when all you have to compare is a treatment group versus a non-specific control group, then you cannot be certain that the good results are do to the test agent. Good results might simply reflect the effects of good general care and the "placebo effect" in wound healing that results from good general care. The corollary to this is that you must never confuse normal healing and good care with a response to the test product. Remember, many physicians and nurses have never witnessed proper wound care and normal healthy wound healing, and many have never once in their entire careers prescribed proper care. On the contrary, many have prescribed completely improper, erroneous, damaging, and destructive care that perpetuates the wound and its problems. So, when they get to witness normal natural wound healing at normal natural rates because somebody prescribed or implemented some basic hygiene to keep the wound healthy and allow it to run at its natural rate, they think they have just witnessed a transcendent miracle. This evangelical approach to wound product marketing is all too common. Unlike overtly and knowingly bogus patent medicine claims, the claims from this kind of experience can be in good faith, with the wound naives genuinely believing they have witnessed the hand of an angel in the potion they have prescribed.

An example worth mentioning is the famous "Steed study" (***1:*** *Steed DL and the Diabetic Ulcer Study Group. Clinical evaluation of recombinant human platelet-derived growth factor for the treatment of lower extremity diabetic ulcers. J Vasc Surg 1995;21:71-81.* ***2:*** *Steed DL, Donohoe D, Webster MW, Lindsley L, and the Diabetic Ulcer Study Group. Effect of Extensive Debridement and Treatment on the Healing of Diabetic Foot Ulcers. J Am Coll Surg. 1996;183:61-64*). This was one of the pivotal studies that allowed Johnson & Johnson to bring PDGF to market (Regranex®). It looked at the use of this topical drug for diabetic foot ulcers. In analyzing the data, it was found that frequent periodic wound debridement had a significant beneficial effect on healing rates and outcomes. Regular periodic debridement beat standard care. PDGF beat standard care. Debridement plus PDGF was even better. What does this teach us? When Regranex® is used, the wound surface must be prepared by curettage or other mechanical debridement (this removes the inflammatory layer of the wound which has proteases which would destroy the drug, and it also exposes the angiocyte and fibroblast responder cells directly to the drug so that it is not wasted by buffering from non-relevant cells or matrix). Good wound studies should have three arms, a well defined "standard care " group versus a protocol placebo group versus a protocol drug group. It is easy to see how any poorly designed wound study that has just "test" versus "control" groups could be a mistake. Imagine a control group (without the test drug) that has just "basic care" with a generic dressing, never bothering to do the curettage. If the investigators only did curettage when the test agent is applied, and not otherwise, then the effects of debridement versus test agent would be analytically inseparable. If the investigators were unaware of this issue to begin with, they would falsely conclude that good results were due to the test agent. The Steed study (an early but good study in this young business of modern pharmacological wound care) did not have three groups, but it did at least analyze the data that way. In so doing, it uncovered not just legitimate evidence for the positive effects of topical growth factors, but it strongly illustrated the value of regular wound hygiene and debridement. Regranex®-PDGF is an important product, one of the few validated wound stimulatory therapies that we have. However, assume for a moment that it had no useful effect beyond good "placebo care". It is easy to see how the effects of good preparatory care could have been misconstrued as an effect of the test agent.

You are probably saying though that "all good double blind studies should be precisely detail-for-detail matched in technique, except for placebo versus product X in the medicine bottle, and if that were true, there would be no need for a third arm, and such analytical traps would be preempted". True, but in wound studies, exact matching of groups is often impossible, and so too is blinding the product or investigators – that is just the tangible reality of many wound care items and modalities, and that is why a third arm is needed for many clinical wound product studies. Thus it is up to the investigators and their protocols to be as exact and detailed as possible, to foresee all statistical pitfalls and design around them, but alas, such is often not the case. It is also the duty of the FDA to be discriminating about such details and catch the deficiencies, but when the regulatory body has no expertise on the subject, they can be no better than the imprecise investigator. The reality is that there are many wound products on the market that have bad studies behind them, purporting to show meaningful data when all they have is garbage. Just because THEY said it, doesn't make it true. When bogosity slips through the investigators, the regulatory agency, and the editorial boards, the last line of defense against irrelevant and erroneous products is YOU, the discriminating wound product user and prescriber.

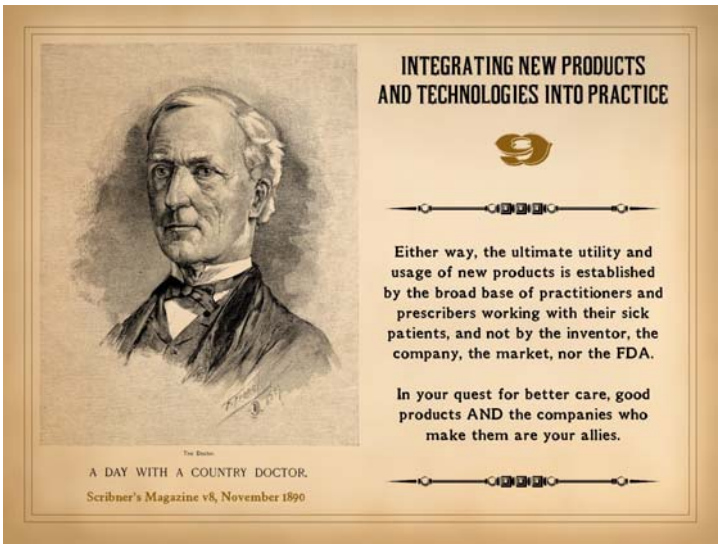
Finally, with regard to bogus data, remember that some meritorious products may have little to go on in the early days of their development. A

product does not get to market without evidence, sometimes robust and voluminous, sometimes rather limited. However, it does not even get to the point of being a potential product in front of the FDA without some kind of preliminary evidence that curried the interest and efforts of inventors, investigators, and investors. Keep an open mind and use your knowledge and analytical skills to sort wheat from chaff based on the available knowledge. For a new or potential product, little data but with a rational and believable concept, presented by moral and intellectually honest people is okay. Such concepts and potential products should get your respect and some of your time to hear about them.

Bogus marketing is of two kinds, erroneous but excusable versus disingenuous. The trade card for Henry's Carbolic Salve was of the former. It attempted to sell, but it did not attempt to deceive. It made unsupported and overboard claims, and it embellished whatever truth there was with unbridled zeal, but it was all done through the filter of the pseudo-legitimate knowledge-of-the-day. The pitch was made in sincere good faith. It was honestly well intended. They hoped to make money selling you something that seemed to have promise to do what they claimed. When the Pure food and Drug Act of 1906 was established, the government basically said "prove it" – no unsubstantiated claims – prove it. So products like Henry's could not survive, because they could not prove it – either there was no proof, or else small potatoes companies could not muster the resources to prove it. The same remains true today. "Proof" in this business is a complex and expensive affair of corporate, professional, and social engineering. Without monetary resources and a good pitchman to raise the initial capital, even the best ideas sink into oblivion. Products that do make it to market must be sold, to recoup investment and then make profits. Good companies with good concepts succeed by delivering good products, and everybody wins. However, if the product is marginal or bogus, but everybody honestly buys into the bogus data, or is blind to the faults in the proof, and if they genuinely believe in their "proof", then they will have an honest enthusiasm trying to sell what they believe is good. The product may be bogus nonetheless, but this kind of good faith use of erroneous or misunderstood data should not engender any disrespect. Try to communicate your thoughts and analysis to the company. Good companies listen (see Apligraf above, slide 34), and eventually it might be re-engineered into something good, or it might go away. In the end, it is YOU, and only you, the discriminating prescriber of wound products who drives the ultimate market for any product. If a product is no good, honestly or dishonestly, just don't prescribe it.

The dark side of bogus marketing is the disingenuous kind, knowingly false and deliberately deceptive. Under the regulatory laws of the past 100 years, a company cannot just simply make outlandish claims and tell outright falsehoods. To deliberately and deceptively bring a bad product to market and then strengthen that market by blatantly dishonest miscommunication with professionals, prescribers, patients, the public, and even the government regulators, that takes a deliberate and well-crafted stratagem. And as we have seen recently with a number of high profile criminal and civil liability actions against several pharma companies and medical device manufacturers, some companies or their top executives seem to have no morals or boundaries these days. My earlier statement that companies are not inherently evil remains true – they are big organizations with many honest dedicated unimpeachably decent employees – but that does not prevent a few immoral executives or boards from selling their souls on the ride to the top. Sadly, we are hearing more and more in recent years about illegality, deception, and moral betrayal from these companies. How do they do it? How do they get bogus data and marketing claims past regulators? If you exclude the cynical answer of "corruption in the highest places", they do it with statistics. Not real statistics. Bogus statistics. As in "there are three kinds of lies: lies, damned lies, and statistics". (This quote was mentioned by author Mark Twain who attributed it to Prime Minister Benjamin Disraeli, although the true origin is actually not certain.) Data can be engineered – massaged, tweaked, edited, redacted, revised, refined, reinterpreted. The data may be numbers, spreadsheets, photographs, testimonials and endorsements – any type of pseudo-technical information that can persuade someone else under the mien of professional and scientific legitimacy. Wiley disingenuous folks bent on market success and profitability can make data say anything they want it to, anything they want you to hear. And if the regulators aren't sufficiently savvy – and for wounds they aren't – then they can persuade almost anybody about almost anything. "Our company is righteous. We don't tell lies, neither little fibs nor white lies, nor massive fraud and scam. We tell neither the little lies nor the damned lies. No, we don't ever lie, we don't need to, we have statistics, and we can make them say whatever we want." If you haven't read about the Pfizer criminal settlement, you should – the details are dismaying but instructive about the pitfalls in the modern "ethical pharmaceutical" industry, including the "evidence based" tactics as well as the salesmanship tactics that created such a big deceit.

There are plenty of bogus products, for wounds and otherwise. You need to discern the bogus and say bye-bye. However, you do not want to overlook the "gem in the rough" when a potentially good product has only limited or bogus data. So again, it is up to YOU to be knowledgeable, discriminating, and have an open but wary mind. Of course, good companies have their own responsibilities too. If they have a good product but bogus data, they owe it to themselves and to all of the potential beneficiaries of their good product to get better unbogus'ed data so that their claims have more power. I am always looking for the next great product, something that helps me get better results faster, and so are you. However, there are only so many hours in a day to study any of this, and there is a constant barrage of noise in the wound and medical product marketplace. Amidst the din of it all, amidst the clutter & noise of hundreds of products, claims and pitches, the good companies with good products need to give me something to go by to make me notice and persuade me to try them. But I also want to ignore the phonies and the hucksters. How do I tell whom I should give my time and consideration to? Dr. Cheatham's Bogosity Matrix. Just remember, regardless what the company screams at you, regardless what 4-color printed drivel they shove under your nose, a product is either legitimate or not, and it either has good data or limited data. For each product or company, figure out where the product sits in that 2x2 cross – legitimacy versus proof – and then you can analyze the product based on the various issues discussed here.



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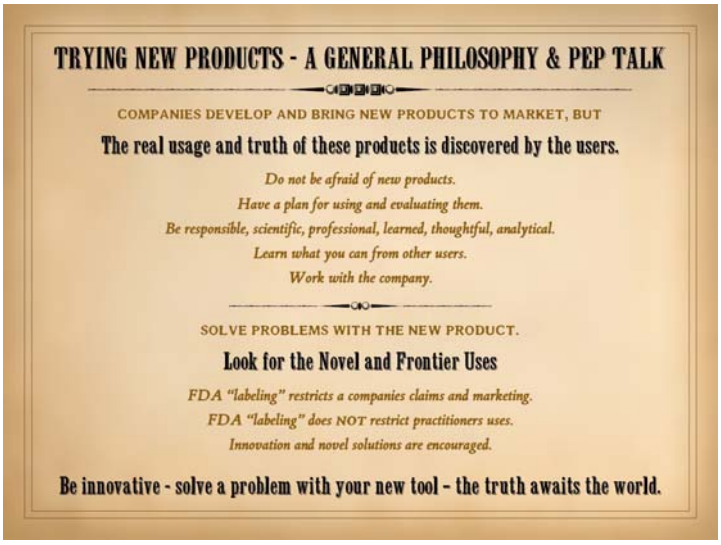
Integrating New Products and Technologies into Practice #9

General morals, principles, and preparation for a new product.

New products are good or bad, bogus or legitimate. Either way, they must prove themselves. Ultimately, the validity and utility of new products is established by the broad base of practitioners who use and evaluate them as they try to make their sick patients get better. The ultimate place for each product, its ultimate persistence or demise, is determined by the marketplace of professionals who prescribe it, and not by the inventor, the company, nor the FDA. The companies will try and persuade you, and regulators and payors will interfere with good practice, but ultimately the real value of products is decided by you and us. For any subject or problem, if you are satisfied with standards of care as they are and see no need for improvement, then you do not need a new product. But if you quest for better care, then new knowledge and good products are the only agents of change. Good products and also the good companies who make them are your allies in these endeavors.

Illustrated is the doctor, from "A Day with a Country Doctor", Scribner's Magazine v8, November 1890. There is an attitude with many new things in medicine that the drug-device-technique-whatever is founded on arcane specialized knowledge or else requires such extraordinary dexterity that only the special few are smart enough or skilled enough to use the gizmo, typically academic elitists in their venerable ivy halls and ivory towers. The reality is that, except for a few highly centralized services such as organ transplant programs, all good care filters down to "the street", where the country doctor in all of us takes care of real people with real problems. Most concepts and products in wound care are very accessible. All that is expected and required of the practitioner is to be knowledgeable and discriminating, to remain in charge of your own assessments and conclusions about whatever is new.



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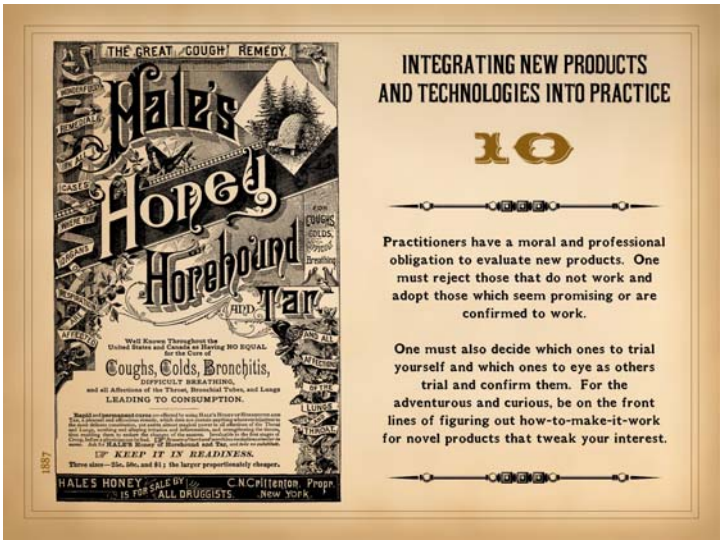
To reiterate, companies develop and bring new products to market, but the real usage and truth of these products is discovered by the users. As a matter of general philosophy and a pep talk about you and your relationship to new products, here are a few points. **Do not be afraid of new products.** If they have made it to market, they are mostly safe if used properly, and they have some nominal validity. If they make sense to you, try them. **Have a plan for using and evaluating them.** Do not just dive in and prescribe indiscriminately. Work through in your mind your exact technical use of the new product, what problems to anticipate, and how to set up your staff and office logistics to use it. **Be responsible, scientific, professional, learned, thoughtful, analytical.** This is the only hedge against bogosity, harm to your patients, and waste to "the system". **Learn what you can from other users.** They will help you get going, and even when you are very familiar with the product, others might show you new uses and pathways to better results. Likewise, help the novitiates, and share what you know with others. **Work with the company.** While you must remain in charge of your own assessments and conclusions, the company can be your best source of meaningful new knowledge. Even when a product is bad, information and resources from the company can be the fastest way to come to a proper negative conclusion and abandon it. When the product is good, the company and its reps become your partners in delivering good care to patients with real problems.

If a new product has merit, then ideally you should be looking for ways to get the maximum value and utility from it. This principle may lead you to novel insights and uses, extended applications, and better or more efficient results than what the original developers and manufacturers had envisioned. Do not be afraid of innovation. Do not shrink form the role of innovator. In the United States, the FDA regulates what a company may claim and how the product must be labeled, and it restricts how the product may be marketed, all based on the scientific studies and proof presented by the company. None of this restricts innovation by licensed practitioners, and novel uses of established products is recognized as one of the important means of progress. Remember that innovation and the advancement of knowledge have been cherished principles in medicine for a very long time. Physicians swear an oath upon graduation from medical school, the Oath of Maimonides from the 12th century being a popular one which includes the lines, *"Grant me the strength, time and opportunity always to correct what I have acquired, always to extend its domain; for knowledge is immense and the spirit of man can extend indefinitely to enrich itself daily with new requirements . . . Today I can discover my errors of yesterday, and tomorrow I can obtain a new light on what I think myself sure of today."* So, when it comes to new knowledge, concepts, techniques, technologies, products, and devices, be receptive, but especially be innovative and solve a problem with your new tool. The truth you find awaits the world.



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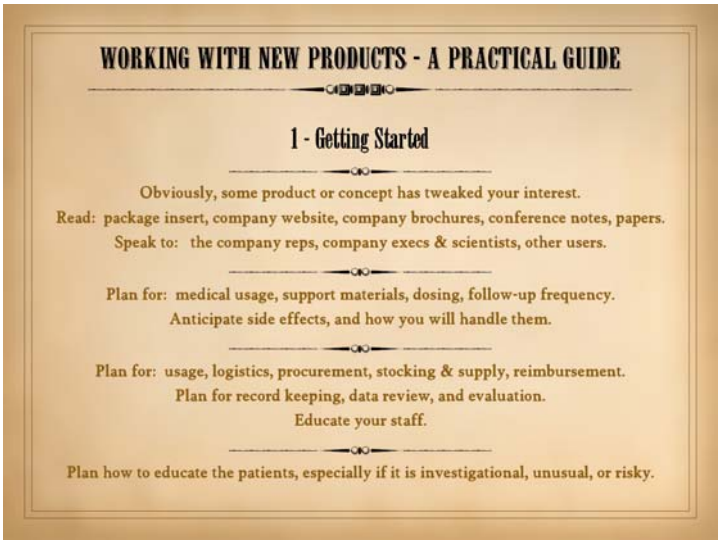
Integrating New Products and Technologies into Practice #10

Integrating a new product into practice, step-by-step & details.

Practitioners have a moral and professional obligation to evaluate new products. One must reject those that do not work and adopt those which seem promising or are confirmed to work.

One must also decide which ones to trial yourself and which ones to eye as others trial and confirm them. For the adventurous and curious, be on the front lines of figuring out how-to-make-it-work for novel products that tweak your interest.

The philosophy behind all of this now leads into some pragmatic suggestions and guidelines about hands-on work with new products.



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Obviously, some product or concept has tweaked your interest. So, here is a practical guide to working with new products.

1 - Getting Started

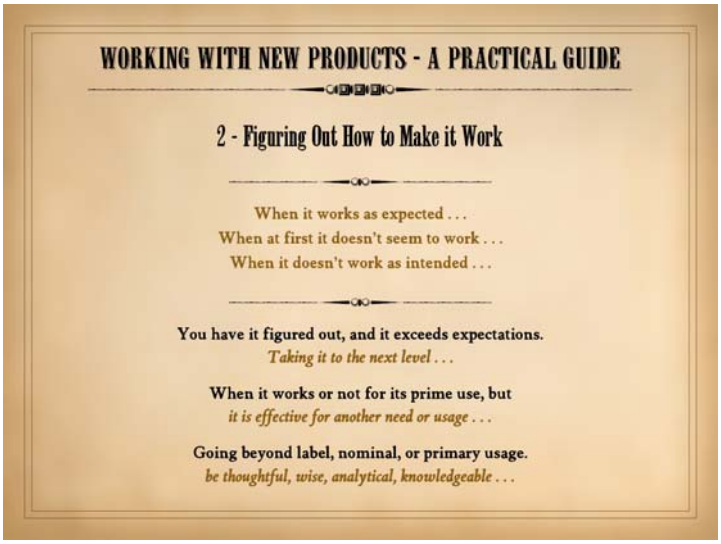
The first thing to do is get relevant information. Reading the package insert is always a good start. The company website, company brochures, and materials supplied by the reps always risk having some bias and bogosity, but they will also have valuable information. If you can access conference notes, journal papers, and other peer-to-peer communications, do so. In our modern era of information and internet technologies, getting information is easy. Also, speak directly to the reps, and if they cannot answer your questions, they should be willing and able to get you connected with company execs & scientists (if they cannot or will not, that is a bogosity alarm). Obviously, peer-to-peer discussions with other users is the best information, but only after you have prepared yourself with the basics.

Next, plan for the technical medical use of the product. Plan for the actual techniques of administration, the required preparatory care, the required support materials and paraphernalia, the means of delivery and the dosing, and the after care and follow-up frequency. Anticipate side effects, and how you will handle them. For example, consider the use of botulinum toxin for lupus angiopathy (slide 6). When I first heard about it, it made sense and seemed like something worth doing, and it has certainly proven itself. I did my first case within weeks of first hearing it presented at a hand meeting. However, before doing it, I had to answer these questions: how many units to use on each hand; can two or four extremities be done together; what are the dose limitations; where precisely will I inject; how much injectate or drug at each injection point; what pattern of injection to maximize therapeutic result without paralyzing the muscles in the hand; what to do if there is any palsy; how to make the procedure comfortable in the face of dozens of individual needlesticks. This was all easy to figure out, but it is best to do so in advance of the actual event.

Next, plan for the pragmatic and logistical use of the product. The product you want is not magically teleported into your hands at the moment you need it. You need to plan its procurement. If it is a new-to-market product, count on a bunch of payment-reimbursement bugs. It may require extraordinary materials support, e.g. a refrigerator or freezer, a centrifuge, a big roll-around cart, or lots of shelf space, If you practice elsewhere than your own office, it may need to go through a product committee. Purchase orders, paperwork, and billing procedures all need to be considered. These issues are less relevant for smaller, safer, cheaper, more basic me-too items, but they become all important for novel, risky, and big-ticket items. Almost any reputable company will do, or help you to do this grunt work (getting the product into your hands and then onto the patient is the ultimate closure of "the deal" for them, so they work hard at this; if they do not help with these activities, bogosity alarm). Also, you must plan for charting and record keeping issues, If you intend to review your results or collate your experience, possibly even write a paper or report at a meeting, then plan in advance for keeping the relevant data. Finally, your staff must be educated on all aspects of this, since they will need to do most of the nuts-and-bolts work that gets the gizmo in your hands and onto the patient. Educating home health agencies and other allied providers may also be crucial.

Plan how to educate the patients. Anyone in practice knows that patients and families have a variable capacity to understand or interest in learning about their care. For simple safe products, not much discussion may be needed. For many patients, wound goo is wound goo, and the "red tube" versus the "blue tube" is as sophisticated as it will get for them, so do not go overboard on new product education where it is not relevant. But when it comes to new products, a few important technical challenges and morality issues must be addressed. If the treatment is complicated or requires numerous visits or technical activities, especially those that require direct patient participation, then more explanation is

required. Even if the patients simply need to come to clinic daily for some service, they need to buy into that before committing to a course of care. None of this benefits anyone if the patients drop out of the care before it is completed. For willing and able and committed patients, technical education may be required for the home based activities they will do. When a treatment is investigational, unusual, or risky, then some sort of disclosure is needed. Institutional review boards and ethics committees may be required for hospital based practices and investigative protocols. For products already approved for market, disclosure in a legal or moral sense may not be mandatory, but if the product is new to you, then depending on the circumstances, the patient, and your own disposition you must decide how much to tell them, just as you do daily with well established products and procedures.



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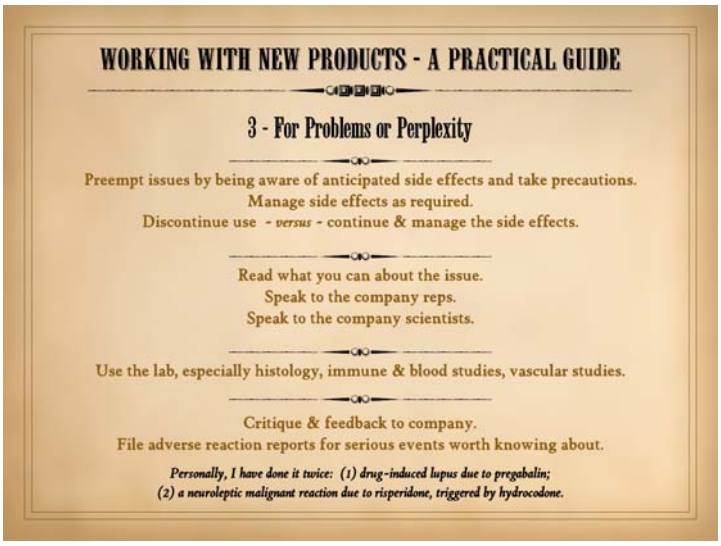
So, you have started using a product, getting it on line and ironing out basic usage. Maybe it is working as expected, maybe not. After your first few experiences with it, where do you go next with it? It all depends if it is working as expected or not.

2 - Figuring Out How to Make it Work

When it works as expected, then good. It is a good product, honestly promoted, properly educated, with everybody doing their part as required. Whether or not it is a major product or a minor product, something to be used frequently or for big problems versus not much is up to you, but now you know you have a useful and predictable item for your toolbox. **If it doesn't work as expected**, the problem might be with the product or it might be with you. Do not indiscriminately abandon it after just one or two trials. The product got to market based on some credible evidence. Many very important, in fact revolutionary products are still not used by those who should be using it, even when mostly everyone else is, and the excuses are often of the variety "it sucks, it doesn't work". But when you listen to how they describe their use of the product, they are doing everything improperly. Nothing can fix a bad attitude, and ultimately some products really do suck, but if at first things seem wrong, review everything about it. Reread and re-listen how to use it. Rethink the details about its application. Listen and speak to others who are successful with it, and be ready and willing to change how you use it to match those who get good results. Sometimes the buzz about new products is just faddism and the madness of crowds (deliberate reference to *Extraordinary Popular Delusions and the Madness of Crowds*, a treatise on popular folly by Charles Mackay, 1841, something worth reading if you want to understand the perversions of group psychology which lead to erroneous over-the-top enthusiasm for some new products or concepts). Fortunately most of the bad products will soon enough fall by the wayside, although aggressive marketing to deliberately targeted naive consumers can and have kept some bad products alive for decades. So, if it is really bad, that will prove itself eventually, but just because it didn't work as expected the first few times, draw no immediate conclusions, review the details, and try again to make it work. **And what if it doesn't work as intended?** Good, it still works. Maybe it works for the nominal indication, but it took real users like yourself to see that the details of use need modification. Maybe you or someone found a new use or indication that was not originally intended. Many great products have developed that way. If it is working for you in ways different than promoted, you have some obligation to pass this information along. Discuss it with other users. Present it at a local grand rounds. Submit an abstract to a national meeting. Discuss it with the company reps who will then get you in contact with influential people. Good ideas and results need to be circulated, so do it.

Assume now that you have started using a new product, it works well, and you have rolled it into your regular practices. New products become the most fun when they do more than expected, or you have some new insight or discovery that pushes the frontiers of good results. If **you have it figured out, and it exceeds expectations**, then take it to the next level. The company and its reps are the first people to talk to. If some data collection or development effort is needed, they can and usually will help. Presenting your work or findings is also crucial, and this is done initially via presentations at meetings, and then, if you have enough quality data, via journal articles. The same is true when you discover that **the product works or not for its prime use, but it is effective for another need or usage**. Speaking to the company for some monetary support to do your scientific investigation is usually easy to arrange. The companies are looking to expand their markets and indications, and investigator initiated studies or pilot studies are cheap in the big scope of things. Remember, in spite of those stupid waivers that political correctionists want you to sign, no medical product comes to market without the company that makes it spending money on legitimate clinical testing, and that means money paid to institutions and professionals. The companies and their products are not evil. In spite of a few high profile reports of scientific fraud in recent years, investigators and their host institutions (and that means you) are likewise not evil. Yes some products and indications are lame or bogus, so professional users have to make intelligent informed choices. But every great product that has made a significant difference, a significant advance, has started with some dude in the trenches with some idea about some gizmo, and some company fronted some cash to get the idea off the ground. That dude could be you. When you discover something good, make it count. Finally, do not be afraid of **going beyond label, nominal, or primary usage**. The difference between regulatory controls on manufacturer's claims and marketing versus the rights and obligations of licensed professionals has been discussed. Your professional credentials and licensure expect that you will be knowledgeable, thoughtful, wise, and analytical. Every time you apply any treatment, do any procedure, use any medication or product, it was some other envelope-pusher before you who did it first, and then everyone else established it as normal practice. You too can be the innovator.



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You have now established the new product in your practice. Perhaps you are doing novel things with it and spreading the word. Though all of this there will likely be some problems or perplexity. They might be unexpected complications or caveats. They might be difficulties getting product delivered to the patient, or getting authorization from payors who have no knowledge of this new product. What do you do?

3 - For Problems or Perplexity

With regard to unexpected medical issues, preemption and prevention are best, by anticipating side effects and taking precautions. When expected or unexpected side effects occur, manage them as required. This is no different than for any other product of established usage. If you are the first to observe, treat and report on a side effect, then you are the innovator. Sooner or later good new products become established therapy, and the side effects and problems are well known. But in the early phases of using new products, recognizing and treating the problems are part of the whole discovery. When problems are relatively serious, you have to decide whether to discontinue use versus continuing and managing the side effects. Nausea, hair loss, and life-threatening neutropenia are expected side effects of cancer chemotherapy. We accept them and vigorously manage the life threatening risks of therapy, because ultimately the cure is hoped to be better than the disease. Wounds do not have the same life-and-death implications as cancer, so perhaps we are unwilling to use potentially lethal wound therapies, but the balance of risk-versus-benefit governs all therapeutic decisions. The more that a good treatment makes a big difference, the more important it is to learn how to manage side effects and see the treatment through to the end.

Of course, odds are that others are starting to have the same experiences and learn the same lessons that you are. So, read what you can about the issue and speak to the company reps. For any reputable company that I have ever worked with, if there is an unexpected issue of clinical or scientific relevance, the reps will get you connected with scientists and medical directors in the home office. They will have more information about the subject, or else be willing (often enthusiastic) to hear about what you have discovered. Of course, the adverse event that you and your patient experienced may be new to everyone, and there will be no answers nor knowledge other than what you can glean. So, do not be afraid to get blood tests, biopsies, imaging, consultations, or whatever to try to elucidate answers and solutions where none existed before.

Critique and feedback to the company are crucial. The past decade has seen a few newsworthy events of fraud and criminal activities by certain pharma and device manufacturers, such as the brouhaha over cox-2 nsaid's. Thus, while the companies are generally not evil, the professionals need to be especially on their toes these days. When you communicate to a company that there is a problem with a product, my experience is that they will take it very seriously. If your adverse event was a one-time idiosyncratic thing, then that is interesting, but just "so what" in the larger picture. Odds are though that other users will have similar adverse events, and if everyone provides critique and feedback, then the significance builds, and the companies themselves will incorporate relevant warnings and advice in their communications. However, even the best companies have an inherent conflict of interests, between sales versus the disclosure of minutiae. So you, as the professional, have other channels of unbiased and protected reporting. Presentations at meetings and in journals is important when you notice peculiar problems and trends. Remember, complications are not necessarily a proscription against use, just a warning that some other caveat needs management. Learning how to anticipate, avoid, and manage the complications is part of bringing any good new product into wide use and acceptance. That is what Withering did with digitalis.

When a complication is particularly noteworthy or serious, regulatory agencies should be informed. There are plain and simply some bad or dangerous new products that come to market that should never have, and if you recognize them, you should do what you can to share your insights with those that can take corrective action. However, the bad dangerous scenario is very rare, since in principle the FDA regulatory process ensures at least the safety of medical products (unless the company illegally scams the process, which is the basis for recent penalties against certain companies). What is more common is that proven good products have some weird incidental adverse event, not likely to recur for any single practitioner, and thus not big enough to become a journal article, but nonetheless worth having on record for others who have had a similar event and need to know if that drug or device might be the cause. I have twice filed official adverse reaction reports for serious events: (1) a case of drug-induced lupus due to pregabalin, and (2) a neuroleptic malignant reaction due to risperidone, triggered by hydrocodone. With all new products, you decide. Do you wait for others to test the waters and figure it all out, and then you adopt it when it seems fairly standard? Or, do you become the early user because you understand the problem and the therapy and find it intriguing or worthwhile? If you are the early adopter, your professional credentials, morally and ethically, even if not legally, obligate you to observe, collate, and report your own experience, both good and bad.

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This slide tells two short stories of working with two companies and two products. The simple message is that the best interests and good fortunes of the patient, the product, the physician, and the company are all intertwined. When you are working with a credible product and a good company, you can expect good rapport and liaison between physician and company to solve medical, technical, and logistical problems that might arise. Both of the products profiled here, Fibrinet® by Cascade Medical, and Apligraf® by Organogenesis, have been discussed on prior slides (6 & 32).

Fibrinet®: As a new product, we were excited about the science and pre-clinical data behind Fibrinet® platelet-rich fibrin matrix. We wanted to begin using it as a stimulatory wound healing agent for outpatient use. However, although it is easy to use, it does require specific equipment and procedures, and it could not be used until the equipment was present, the staff had been trained, and payment and reimbursement issues had been solved. The problem for many new products is that if a third party payor does not recognize it, and thus it is not reimbursed, then it is not affordable for the patient. The fact that many new medical products are priced beyond the means of most users is a separate socio-economic issue that you will have to ponder for yourself. The conundrum is that payors often do not approve a product until it is "proven" with a large clinical experience, yet that experience cannot be forthcoming until the product is approved and thus available for large numbers of patients. This particular platelet product is priced competitively compared to other platelet products, and it is a bargain compared to other wound stimulatory products that we use (1/3 – 1/2 the cost of clinically comparable biologics). Nonetheless, as a new product, it is not "covered" by the payors, and most patients could not afford it from their own pockets. A new company trying to promote a new product should be willing and ready to offer product for free or at a steep discount in order to get prescribers to experience it, and the cost-to-the-company should be part of their capital investment and the "cost of doing business". However, companies do not survive without revenue, and for small start-ups with just the one product, gratis "freebies" can only go so far. So, the company and the prescriber have to cooperatively understand each others situation and plan strategically, based on the local payors, hospital or clinic procurement and reimbursement practices, and other such factors that are categorically unrelated to the core medical issues. Any company serious about making a new product successful will work closely with their "pioneer" prescribers.

For Fibrinet®, there were two issues that needed attention before using the product. The first was a technical issue. This is not a product where you just peel the package and apply. Blood must be drawn from the patient into the tubes and various paraphernalia of the product. Then, the blood must be processed by a two-step centrifugation. Providing the special centrifuge and then training the nursing staff were prerequisites to use. The company did their homework in having an OEM centrifuge manufacturer make a machine to their specifications, and the company was then able to supply us with the machine at a partially subsidized cost. The company staff flew to our facility for hands on training – very thorough and well done. User-prescribers should expect this kind of quality customer support from any company serious about their product. The second crucial issue was costs and reimbursements, always a thorny issue for worthwhile but expensive new products. Working through the payment details required close liaison between our clinic administrative staff and the company, and that support came not just via the company reps, but directly from company executives. Our ability to use the product initially came from a batch of free product, and then product at a discount. Concurrently the company had ongoing activities to persuade payors to make the product "formulary", a persistent necessity for any company with a new product. Currently, our ability to prescribe the product is still hampered by limited payor support in our particular geographic market. However, our own clinic staff also works this issue, case-by-case, by discussion with the payors and appeals on individual cases. The net result is that a product that we have seen compelling results and have great faith in remains elusive for us. The "freebie" grace period is over, and we use the product when we can arrange proper reimbursement, but we cannot use it as much as we would like. The battle goes on.

Apligraf®: Our second short story is about Apligraf®, another wound stimulatory agent, and one of our favorite products to use for relevant indications. This product has now been on the market for about 12 years, and its technical support, procurement and reimbursement issues, formulary status for the payors, and other such logistical issues were ironed out long ago. We still cannot use it every time we want, because of payor-reimbursement issues, but the denials these days are relatively few. This is a living cell biologic, and it is manufactured with an extraordinary amount of safety testing to make sure that the donor cells are free of any known pathogen. The product is also proven in clinical practice, with rare incidental and anecdotal problems related to its presence on the recipient wound. Recall that purified PDGF is a therapeutically comparable product. Over the years, we have seen several incidental contrary reactions to PDGF, where its use has resulted in rapid intense inflammation and re-ulceration with enlargement of the wound. We have observed this exclusively in patients with connective tissue disorders, with or without concurrent hypercoagulable states. This might have been unexpected, but it is not all that surprising in these patients who have bizarre immune and inflammatory profiles to begin with. Many other patients with these disorders have had PDGF with complete safety or effectiveness, so this adverse event is very incidental and unpredictable, but we have learned to be wary of using purified PDGF in our rheumatoid and lupus patients. For a number of years, we had not observed a comparable event when using Apligraf®, so we therefore tended to use Apligraf® preferentially for autoimmune wounds whenever we wanted to use a biological stimulant, meaning we have had a large and safe experience with Apligraf® in these patients. But then it happened, just once, then not again for two years, and then we had two such adverse events within a month of each other. The latter two cases are illustrated.

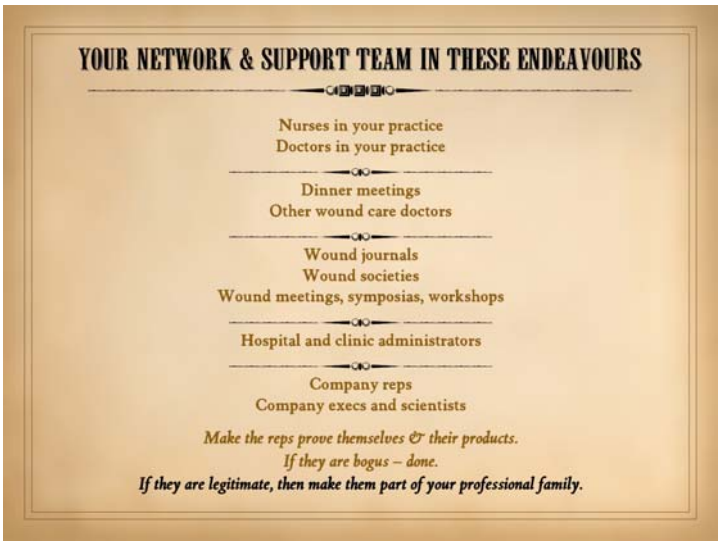
Top is an 81 year old woman with a chronic ankle ulcer following excision and radiation for melanoma. ***Left*** is the wound after miscellaneous activities reduced the original large wound to a small area over the tibialis tendon. Apligraf® to stimulate the remaining area to close was a typical choice for us under these circumstances, and considering the good uncomplicated improvements already made, we expected the Apligraf® to carry this wound "across the finish line". As a radiation wound in a patient with no other major diseases, immunopathic adversity

would not have been expected. At about three weeks after placement, the wound became painful and inflamed, and there was progressive ulceration. The ***middle*** image shows the wound at 4 weeks at the peak of these events. Remaining material was removed and daily topical care was restarted. ***Right*** is the wound 4 weeks later, the wound back under control, but the damage done. Subsequent wound histology showed extraordinarily dense perivascular infiltrates with lymphocytes and plasma cells. Whether they were present before or induced by this turn of events (cause versus effect) cannot be inferred, but this is the histological profile indicative of wound immunopathy that we can equate with risk of this kind of reaction. The question was whether this represented a non-specific immunogenic reaction related to standard wound immunopathy, versus an HLA-type of donor-specific rejection (even though the graft does not have leukocytes nor significant HLA antigens), versus some type of induced acute inflammation or thrombosis. Not having taken any biopsies at the peak of the event, this question cannot be answered. **Bottom** is a 50 year old woman with a chronic ulcer due to a primary hypercoagulable disorder with secondary venous stasis. Her wounds healed with anticoagulation and compression, but inconsistent follow-up and maintenance care caused late recurrence. Shown ***right*** is the leg after miscellaneous activities reduced the original large wound to the area shown. The story is very analogous to the first case, with no problems for two weeks after placement of Apligraf®, and then sudden inflammation and thrombosis. ***Middle*** shows that the wound at three weeks, infarcted. ***Right*** is the wound 2 weeks later, cleaned up and under control after restarting basic daily topical care, but the damage is done and the wound is bigger.

The events were very suggestive of a delayed immuno-sensitivity reaction. The sensitivity may have been to HLA antigens or maybe to something else in the graft. Absent biopsies and histology from the time of the center images, the events cannot be inferred with certainty, but the events fit with a delayed lymphoplasmacytic response. The indolent nominal uncomplicated progress for two weeks fits. The time delay until response of about 3 weeks fits. The presumption is that once sensitized, then an acute neutrophilic response was triggered which mediated the lysis and/or thrombosis-infarction. In the top case, the inflammatory-lytic appearance of the wound and peri-wound suggests that acute inflammation predominated. In the bottom case, the thrombo-infarctive appearance of the wound, and the relative lack of peri-wound inflammation is consistent with her confirmed history of a hypercoagulable disorder. The lymphoplasmacyte infiltrates seen later in the top case, regardless whether cause or consequence, supports these assumptions. Because these two events occurred so close to each other, it was natural to wonder if the grafts were from the same donor or from the same manufacturing lot, whether there was something inherently antigenic about the donor(s), or some sort of production quality control issue. The company reps have always worked closely with us, and this time was no different. The information and case reports were requested and submitted, and we were soon enough talking to the company's chief scientists. They were very knowledgeable about relevant issues, and we had informative discussions. They did not eschew the possibilities discussed here, but they were able to discuss the various reasons why at least an HLA mediated reaction would have been unlikely. Production lots and donors were different, and they had no other reports of problems. Anecdotal cases are just that, incidental stories, and absent any acute phase lab studies or specimens, nothing further could be learned from these cases. However, the company did offer any support needed for further investigations, including in-house study of specimens, and the next rare time this happens, we will get relevant specimens.

The moral of both of these stories is simply that reputable companies with good products, big and small, startup or staid, stand behind their products and offer the kind of customer support and service that you would want, through all phases of procurement, testing, training, clinical use, and atypical situations. As the customer-prescriber who specifies their products, you should expect no less. Do not ever be timid about asking your reps to get you in touch with company principals and scientists when there is a legitimate reason. Remember, the company's motivations are complex – their investors and employees want profits, but their founders and scientists also want to save lives, cure the world, and see their widgets and projects be successful. You want to cure your patients, and to do so as efficiently and effectively as possible, meaning having the most dependable tools, which come from the companies. The companies want you to prescribe their products so that they can succeed, but never forget that you likewise want the company to succeed so that their good product does not disappear. The better interests of the company, the prescriber, the patient, and even the payor are intertwined, and what is good for one is generally good for all. If you find a new product that you believe in and it helps your patients, and you would hate to see it fall off the market, then you have to help the company make it successful before apathy or third-party-payor barriers sink the product.

What about bogus products? There are bogus products backed up by good responsive companies, especially when the product is of the good faith honest-but-naive variety of bogosity. Of course, if the product is no good and you do not use it, then you will have no need to interact with the company. However, be wary not to be beguiled to use a bad product solely because the people and practices behind the product are otherwise honorable. Bogus companies are to be avoided. You can recognize them by features such as: their reps have marginal or no meaningful knowledge, or they are disinterested or disengaged, or they fail to make follow-up calls or leave samples, or they have no studies, literature, white papers, technical briefs, nor anything else to show you; reps refuse to get you in touch with company higher-ups; the reps have no tools nor interest nor any personal effort or involvement to help with third-party payor or hospital procurement issues; the company is non-responsive to requests for more information; they eschew or deny or have no follow-up on technical or clinical problems or adverse events; marketing and promotional materials are blatant bogosity; the spokesmen and champions for the company (such as doctors on the lecture circuit) have no credentials nor credibility, and are patently unknowledgeable about wounds or the science behind the product.



In the never-ending business of staying current and finding the best solutions for your patients, many acquaintances and associates will be your network and support team. Remember, no person can be aware of every new item to hit the shelves, and even if you could, there is not enough time nor patients to fairly try everything. You will try some things and pass relevant information on to others. Others will be doing the same thing and you will get valuable information from them. Here are you comrades and trusted sources:

If you are a doctor, other doctors are doing what you are doing, getting interested in a product, trying it, learning to use it, and passing on that information. Doctors in your own practice are a vital and a completely trusted source of information. The nurses in your practice have an intense hands-on appreciation of what works or not, especially for items related to basic daily care and patient support. They will know better than anyone how patients themselves adapt to new products. They are a key liaison between you and the other doctors in your practice, reporting on the experiences you all have with the different products you are all trying.

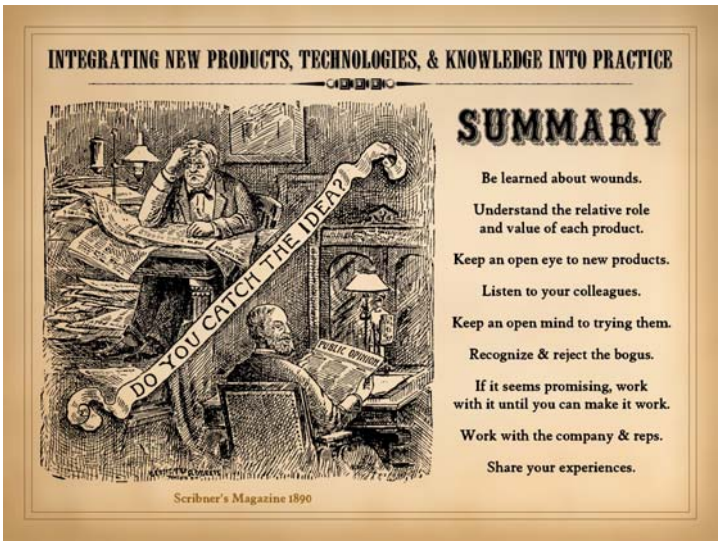
Like any specialty, wound care is a brotherhood, and other practitioners not in your own practice, around the country and around the world, are also doing what you and your immediate colleagues are doing. You will hear from them at meetings and symposia, via journal articles, and other standard means of inter-professional communication. Dinner meetings are especially valuable. They are typically sponsored by a company with something to sell, so the cynics and political correctionists all have some stupid opinion about that. But the doctors who are presenting are just like you – they are doctors who care to get good results on behalf of their patients, and in so doing, got interested in a particular product and learned to make it work. Dinner meetings are intimate, informal, and a good place for honest talk and the sharing of experiences. Here is where you will learn real details about a product, well in advance of journal articles, and in greater depth than you can ever get from a podium speech at a meeting. And always remember, YOU are in charge of what you learn and take away from these experiences, not THEM.

Wound journals and wound societies represent our specialty at the organization level, and every specialty needs them. The specialty of wounds has developed some very good high quality meetings and journals, and everyone with a sincere interest in the subject will find them to be a crucial place for good information about new knowledge, practices, policies, and products. There is an ever increasing number of wound meetings, symposia, workshops. These are somewhere between major society meetings and company-sponsored dinner meetings in terms of intimacy and attendance. The wound symposia I have attended in the past 15 years all seem to be very high quality, in terms of content. I think this is because this is a young specialty of interested, enthusiastic like-minded people who want to crack this nut of making wounds heal. Wound practice is a tough practice to practice compared to many other specialties. It takes dedicated or whacky people willing to do this stuff, and workshops and smaller symposia are where you will get to meet many of them.

The practice of chronic wounds is skills, resources, and time and attention intense. Anyone who has tried doing it as a matter of pure private practice has found it hard. The concept of dedicated wound clinics has been amply validated over the past 15 years. The hospitals and clinics which host these programs are a crucial component of the whole process. The administrators who manage these programs are essential, not just for general operations, but for all provisioning, procurement, processing, purchase and payment, and practice implementation of new products, devices, materials, and supplies.

The products you do use or will use are all made by companies. They have executives and scientists-engineers behind the scenes, and reps on the front line to liaison with you and your practice. A good product backed by a good company with good reps is every bit as vital and valuable a part of your continuing education as the medical schools, professional societies, and educational media. They help you hear about new products. They help you bring it on line, up-and-running in real practice. They help you deal with procurement and payor issues. They get you connected to other professional users so that you can hear presumably unbiased experience from colleagues. Granted, we have all experienced bad products, bad companies, and bad reps. Even when they are inherently good, competition between me-too products can be tedious, boring, and embarrassing to deal with, such as being harassed about just another cephalosporin or just another beta-blocker. Fortunately in wound practice, most of the meaningful products are not direct competitors, and even nominal competitors all have a relative place in the big picture and deserve your awareness and understanding (remember the principles of tandem and sequential therapies). It has been my experience that when potential problems or unanticipated issues arise, that the company scientists and even executives take a very direct and cooperative interest in these events. Remember, that even if you take a cynical view of the execs and business people, that the scientist-engineers are professionals like yourself with the same interest in seeing products created and problems solved. They are all an inseparable part of good wound practice.

When a rep wants to demo a new product, make him prove himself, the company, and the product. Is there legitimacy to the concept. Who is the company behind it? What is the basic research to validate it? What is the clinical research to prove it? Can they answer your questions? . . . at all? . . . with meaningful answers? Can they fix procurement, payor, and patient use issues for you. Is he a portal or a barricade to company resources? Remember, only you can make the ultimate decision about the value of a product. Good products and reps make it easy for you to decide, and so too do bad products and reps. But, for newbies, novel products, and early phase development, it can be harder to decide good from bad, real from bogus. So, make the reps prove themselves. If they are weighed and found wanting, feel free to banish them. If they prove themselves, if they are legitimate, then make them part of your professional family.



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Summary

New concepts, technologies, and products are a fact of life in medicine. Practitioners will always be obliged to evaluate new items, to be neither intimidated nor beguiled by them, to discriminate the good from the bad, the bogus from the real, then decide which to reject, which to accept, and ultimately which to incorporate into regular practice.

Slides 12 – 16 brought an historical perspective to wound products and technologies. About 120 years ago, when the pictured woodcut appeared in Scribner's Magazine, (November, 1890) there were major conceptual changes in medicine that introduced a century of amazing progress. However, chinks have appeared in that system, and while we are now on the verge of an era of great progress in wounds, there are hangovers from this past century which can affect that progress. Beginning about 120 years ago, the concept of pharmacological control of wounds evaporated, while wounds became naively confused with infections. The patent medicine trade was quashed but not buried, and it is rearing its ugly head again. During a time of profound stress on the quality of medical education and medical practice, the confusion and disingenuousness can be easily exploited by those with bogus products. Ultimately, the safety of the patients and the validity of medicine itself rests with the professionals with degrees and licenses. Part of professional expectation and obligation is to make informed good choices about the old and the new. To maintain your intellectual independence, professional responsibilities, and moral righteousness so that you decide what is meritorious rather than being sold by somebody with something to sell, the following are important:

Be learned about wounds. Understand the relative role and value of each product. Keep an open eye to new products. Listen to your colleagues. Keep an open mind to trying them. Recognize & reject the bogus. If it seems promising, work with it until you can make it work. Work with the company & reps. Share your experiences.

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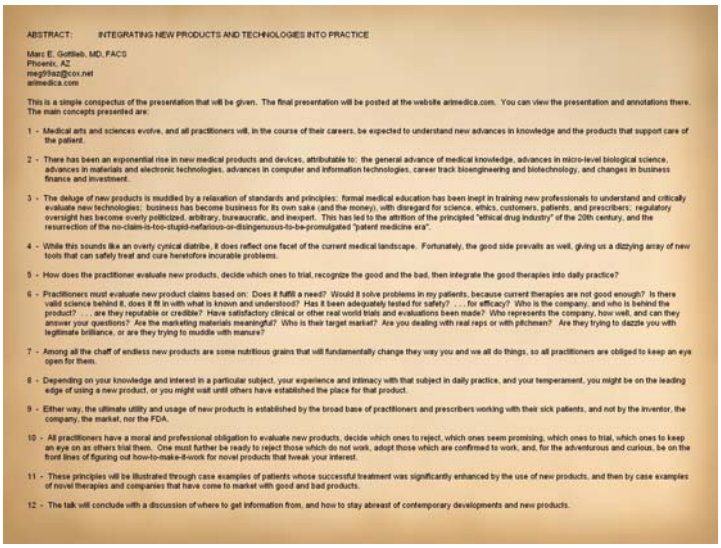
End



ABSTRACT: INTEGRATING NEW PRODUCTS AND TECHNOLOGIES INTO PRACTICE

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This is a simple conspectus of the presentation that will be given. The final presentation will be posted at the website arimedica.com. You can view the presentation and annotations there. The main concepts presented are:

1 - Medical arts and sciences evolve, and all practitioners will, in the course of their careers, be expected to understand new advances in knowledge and the products that support care of the patient.

2 - There has been an exponential rise in new medical products and devices, attributable to: the general advance of medical knowledge, advances in micro-level biological science, advances in materials and electronic technologies, advances in computer and information technologies, career track bioengineering and biotechnology, and changes in business finance and investment.

3 - The deluge of new products is muddled by a relaxation of standards and principles: formal medical education has been inept in training new professionals to understand and critically evaluate new technologies; business has become business for its own sake (and the money), with disregard for science, ethics, customers, patients, and prescribers; regulatory oversight has become overly politicized, arbitrary, bureaucratic, and inexpert. This has led to the attrition of the principled "ethical drug industry" of the 20th century, and the resurrection of the no-claim-is-too-stupid-nefarious-or-disingenuous-to-be-promulgated "patent medicine era".

4 - While this sounds like an overly cynical diatribe, it does reflect one facet of the current medical landscape. Fortunately, the good side prevails as well, giving us a dizzying array of new tools that can safely treat and cure heretofore incurable problems.

5 - How does the practitioner evaluate new products, decide which ones to trial, recognize the good and the bad, then integrate the good therapies into daily practice?

6 - Practitioners must evaluate new product claims based on: Does it fulfill a need? Would it solve problems in my patients, because current therapies are not good enough? Is there valid science behind it, does it fit in with what is known and understood? Has it been adequately tested for safety? . . . for efficacy? Who is the company, and who is behind the product? . . . are they reputable or credible? Have satisfactory clinical or other real world trials and evaluations been made? Who represents the company, how well, and can they answer your questions? Are the marketing materials meaningful? Who is their target market? Are you dealing with real reps or with pitchmen? Are they trying to dazzle you with legitimate brilliance, or are they trying to muddle with manure?

7 - Among all the chaff of endless new products are some nutritious grains that will fundamentally change they way you and we all do things, so all practitioners are obliged to keep an eye open for them.

8 - Depending on your knowledge and interest in a particular subject, your experience and intimacy with that subject in daily practice, and your temperament, you might be on the leading edge of using a new product, or you might wait until others have established the place for that product.

9 - Either way, the ultimate utility and usage of new products is established by the broad base of practitioners and prescribers working with their sick patients, and not by the inventor, the company, the market, nor the FDA.

10 - All practitioners have a moral and professional obligation to evaluate new products, decide which ones to reject, which ones seem promising, which ones to trial, which ones to keep an eye on as others trial them. One must further be ready to reject those which do not work, adopt those which are confirmed to work, and, for the adventurous and curious, be on the front lines of figuring out how-to-make-it-work for novel products that tweak your interest.

11 - These principles will be illustrated through case examples of patients whose successful treatment was significantly enhanced by the use of new products, and then by case examples of novel therapies and companies that have come to market with good and bad products.

12 - The talk will conclude with a discussion of where to get information from, and how to stay abreast of contemporary developments and new products.

Abstract (as submitted in advance of the meeting)

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AND TECHNOLOGIES INTO PRACTICE

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