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Inside

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Technology for hemophilia offers hope for chronic wounds

System also can produce platelet-derived growth factor

New technology now approved in Canada and Europe seems to hold much promise for increased effectiveness in treatment of acute surgical and chronic dermal wounds.

The CryoSeal system provides equipment and sterile disposable containers for rapid automated harvesting of adhesive and clotting proteins from blood plasma to produce cryoprecipitated antihemophiliac factor (AHF), a blood product for intravenous treatment of hemophilia. U.S. marketing of the CryoSeal system for this indication is awaiting Food and Drug Administration 510(k) approval, which is expected within the next few months. Once FDA approval of this indication is achieved, the product's manufacturer, ThermoGenesis Corp. of Rancho Cordova, CA, will make parallel applications for two more indications for the system: production of autologous fibrin glue (AFG) and production of an autologous concentrated platelet-derived growth factor (APDGF) solution for treatment of chronic wounds such as diabetic, decubitus, and venous stasis skin ulcers.

One machine, three functions

The CryoSeal System is a thermodynamic micromanufacturing device that can harvest and concentrate therapeutic components from a patient's own blood. The same CryoSeal device is used for all indications, but each indication requires a different software program and disposable container. The desired material is harvested into the containers. For example, to produce AHF, a technician would put the appropriate disposable container into the machine and activate the corresponding program algorithm in the software. The machine then works with that disposable container to harvest the desired proteins. To make AFG, the technician uses a disposable container called the CP-2 and activates the algorithm for fibrin glue. The machine harvests the fibrinogen protein and thrombin into separate chambers of that disposable disposable container. Production of APDGF requires use of the third software function and third disposable container for the machine. The source material in each case is plasma. In each application, harvesting the desired blood components from the patient's blood takes a little less than an hour.

According to **Philip H. Coelho**, CEO of ThermoGenesis, the FDA approved the first PDGF product in 1998, containing PDGF beta beta. The product, which comes in a gel form, was approved for treatment of diabetic ulcers and has a growth factor produced by the recombinant manufacturing process. "They're basically just growing a growth factor that exists in everyone's body," Coelho says. "Our solution is to harvest multiple platelet-derived growth factors from the patient's own platelet-rich blood plasma and concentrate them, and then bring them to these chronic dermal wound sites for palliative treatment. Using the exact same machine with a slightly different software program, we can get highly concentrated solutions of multiple platelet-derived growth factors including PDGF beta beta." Coelho says these growth factors have been demonstrated to be critical to the endothelial cell growth required to cover chronic dermal wounds.

"Most of these wounds are a result of decreasing vasculature underneath — the blood simply isn't getting to the site — so you need to concentrate them and bring them topically to the wound site," he notes. "All of these treatments for chronic wounds require repeated treatments daily for weeks to heal them."

Product used for hemostasis, wound glue

Cryoprecipitated AHF is normally prepared by blood banks in a labor-intensive two- to four-day process. About 70% of the 1.1 million units of cryoprecipitated AHF now manufactured annually by blood banks and sold to hospitals is used "off label" by U.S. surgeons to stop bleeding and to augment or replace sutures. In this usage, the fibrinogen content of cryoprecipitated AHF is combined with the enzyme thrombin to make a two-part adhesive for surgical hemostasis.

The typical AHF manufacturing process uses five pieces of equipment: a blast freezer, a storage freezer, a 4-degree C centrifuge, an expresser, and a 4-degree C refrigerator. The production cycle involves a lot of handling because the product must be moved from one machine to another in a complicated and error-prone process to manufacture the product from a single unit of blood. CryoSeal products may provide a safer approach to producing therapeutic doses of proteins, enzymes, and growth factors.

The CryoSeal System is a compact, floor-standing unit about the size of a trash compactor, within which a disposable container processes plasma to concentrate therapeutic doses of fibrinogen, factor VIII, fibronectin, and PDGF from a single donor unit of blood plasma. For its use in making AFG, special applicators are provided that allow the surgeon to precisely administer the autologous fibrin glue to the internal wound site to control surface bleeding, bond tissues, and augment or replace sutures.

Autologous fibrin glue contains the adhesive and/or clotting proteins fibrinogen, fibronectin, von Willebrand's Factor, factor VIII, and clot stabilizing proteins, as well as platelet-derived growth factors. ThermoGenesis says its AFG is competitive with commercial fibrin glues derived from blood plasma pooled from thousands of donors.

Pooled plasma raises concern over pathogens

Because of the concern of viral contamination from the source-pooled plasma, it was only in May 1998 that the FDA granted its first clearance to Baxter Corp. for production of a pooled-plasma commercial fibrin glue. Patients who have wounds or other medical conditions that require proteins, enzymes, or growth factors taken from pooled plasma (typically made from a pool of 10,000 donors) for treatment have legitimate concerns regarding the contamination of such products by bloodborne viruses (e.g., HIV, hepatitis A-H, etc.), bacteria (e.g., *Staphylococcus aureus*, *Yersinia enterocolitica*, etc.) and prions (e.g., Creutzfeldt-Jakob disease).

> "If you can get the patient's own body to produce something that they need, there's no doubt in my mind you'll cut down on reactions."

Recent technologies that manufacture these same proteins, enzymes, and growth factors through recombinant production processes rather than pooled plasma have their own manufacturing and allergic reaction safety risks. "Any time we administer any kind of blood products or by-products, there's a danger of allergic reaction," says **Iris Gatchell**, RN, a cardiovascular intensive care unit nurse at Memorial Hospital in Greenville, SC. "If you can get the patient's own body to produce something that they need, there's no doubt in my mind you'll cut down on reactions."

Commercial fibrin glues have traditionally used bovine-derived thrombin in their kits to initiate clot formation. Bovine-derived thrombin is both readily available and inexpensive. With the emergence of Creutzfeldt-Jakob disease (CJD) and nvCJD, however, the European community has prohibited the use of bovine-derived thrombin in commercial fibrin glues.

ThermoGenesis expects sales of the CryoSeal system with the AFG disposable could occur in Europe as early as fiscal year 2000. Nevertheless, formal clinical trials and FDA clearance will be required to market the product for this application in the United States. The company expects to move into parallel clinical trials for the AFG and APDGF product indications in fiscal year 1999, with market launch outside the United States in late fiscal year 2000.

One of the principal investigators in the clinical trials will be **Paul O'Dell**, MD, otolaryngologist and professor and chairman of otolaryngology at the University of Ottawa, Canada, who has tried the CryoSeal system for fibrin glue.

"We've just done a few patients with it and are in the process of setting up appropriate clinical trials," O'Dell says. "My involvement with it was to try it out to see if there were any problems in delivering it or any problems associated with it, which there weren't." Three other Canadian doctors will join O'Dell as principal investigators in the clinical trials.

O'Dell comments that "the problem with the commercial [fibrin glue] products is that they are very expensive. The reason for trying CryoSeal is that it's cost-effective, and with it being the patient's own product, there is no risk of transmitting any of the known infections." He adds that though the patient may spend two or three extra hours in the preassessment unit where the blood work is done prior to surgery, "down the road, the advantage is that if we can glue these wounds closed and don't need to use a drain, the patients may be able to go home right after their surgeries, so that their stay in hospital will be greatly shortened."

The regulatory process has taken about two and a half years so far. "The biggest step is behind us because we've fully characterized all those proteins," Coelho says. "We don't need to do that again. We merely have to demonstrate efficacy for new claims. Basically, the FDA is concerned with safety and efficacy. They want to assure the public that medical claims are supported by the scientific evidence submitted. It's really truth in advertising in a lot of ways. You can't say our product is useful for a surgical glue or platelet growth factor for treatment of dermal ulcers until you can demonstrate this efficacy in clinical trials. That's something I don't begrudge at all. The FDA is playing an extremely useful role in health care, forming a barrier or filter that lets only the products that really work get through."

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Stronger, tougher bacteria force antibiotic crisis

Prescription restraint needed

The wonder drugs we've all taken at one time or another to eliminate the bacteria that make us ill are now a lot less wonderful than they used to be. Generations of exposure to antibiotics, especially the broad-spectrum variety, have made bacteria so much stronger and tougher that sometimes there's nothing left in the medicine cabinet that works against a given microbe. The biggest reason for this increase in bacterial power may be overprescription of antibiotics.

According to a study recently published by **Moshe Arditi**, MD, director, Cedars-Sinai Medical Center Division of Pediatric Infectious Diseases in Los Angeles, controlling antibiotic usage in outpatient settings is now a national priority. *Streptococcus* pneumoniae, bacteria that can cause life-threatening infections and are a major threat to wound care patients, are rapidly becoming resistant to penicillin and cephalosporins such as ceftriaxone, the most widely used antibiotics currently available to treat bacterial infections.

Resistance rates double and triple in one year

Arditi's three-year study of children suffering from pneumococcal meningitis covered 180 patients admitted to eight children's hospitals between Sept. 1, 1993, and Aug. 31, 1996. The study looked at clinical presentation, hospital course, and outcome, taking into consideration the antibiotic resistance patterns of the pneumococci causing the infection. "If you look at each year of the three-year study and look at the percentages, you see a dramatic increase in antibiotic resistance between the second year, for example, and the third year," Arditi says. "In the second year, the penicillin non-susceptible rate [intermediate-susceptible and resistant organisms] was 13%. In the third year of the study, it jumped to 27%. For ceftriaxone, resistance in the first year was 1.7%. In the second year, it became 5%. In the third year, it jumped to 15%. In other words, resistance to ceftriaxone tripled between the second and third year of the study."

The rapid increase in resistance also is obvious when looking at the recent history of penicillin use. For example, 27% of the pneumococci were not susceptible to penicillin in 1996, the final year of this study. That compares to 0.02% reported less than a decade ago, according to Arditi.

There are two crisis-creating forces at work, according to **Farrin A. Manian**, MD, MPH, FACP, hospital epidemiologist at St. John's Mercy Medical Center in St. Louis. One is that bacteria, strep pneumoniae chief among them, are becoming resistant in the hospital setting. "In our hospital, strep pneumonia on the adult floors is probably not fully susceptible to penicillin in about 30% to 35% of cases now. In our pediatric wards, over half the cases are not fully susceptible to penicillin anymore."

Manian says strep pneumonia is the most common cause of community-acquired pneumonia and a very common cause of otitis media. He adds that overprescription of antibiotics by community clinicians, often at the insistence of their patients, is the major culprit in the ability of this bacterium to become resistant so rapidly.

The bacterium most commonly present in patients with chronic illness in hospitals and nursing homes is *Staphylococcus aureus*. This organism, the most common cause of postoperative wound infections, is now resistant to antibiotics in many instances. In the past three years, Manian and his colleagues at St. John's have seen more and more of these *S. aureus* isolates from postoperative wounds demonstrate resistance to the typical antibiotics — semisynthetic penicillins and cephalosporins. "In 1996, about 39% of the wound isolates that had *Staph aureus* in them were resistant to methicillin," Manian says. "In 1998, about 52% of *Staph aureus* are methicillin-resistant. The other big germ we are very much concerned about is enterococcus, which can cause wound infections and bloodstream infections. We have seen a significant rise in the resistance in these kinds of germs." Manian notes the concomitant rise of vancomycin-resistant enterococci (VRE), which is characteristically resistant to just about every antibiotic available. The incidence of VRE in wound isolates has gone up from 12.5% in 1996 to about 33% in 1998.

Touch control is the first line of defense

Manian says the first step to take in addressing this crisis is to institute appropriate touch control precautions — i.e., private rooms, gloving, strict hand washing, and gowning in the intensive care unit to minimize transmission from colonized patients to noninfected patients.

The second step is treatment of infected patients. "This often requires some creative antibiotic therapy, especially with the vancomycin-resistant enterococci," Manian says. "Only one drug works in the test tube: chloramphenicol. It's an old drug that fell by the wayside because of its side effects. For many years it was hardly ever used. Now in our hospital we are using it on a quite regular basis because of the emergence of VRE. We have some isolates that have become resistant to chloramphenicol, too.

"I don't see any immediate solution to the problem," Manian says. "I think it arose for a variety of reasons that are probably going to be staying with us for awhile. We're taking care of a relatively sicker population than we have in the past. People are living longer, they are more immunosuppressed, they're older, and so when they come in a hospital the average patient is certainly a lot sicker than they used to be. They are more susceptible to these kinds of infections in the first place, and I don't see that changing.

"The second factor is the use of antibiotics. Anytime you place a patient on antibiotics, especially the ones who are quite ill and are going to be ill for awhile, you run the risk of having resistant germs emerge."

"Because organisms have a tendency to change their resistance patterns more rapidly than drugs can be developed, new drugs are usually outpaced by the organisms themselves."

Michael Rybak, PharmD, professor of pharmacy and medicine and director of anti-infective research at Wayne State University in Detroit, says there are a number of new compounds in clinical trials, but because organisms have a tendency to change their resistance patterns more rapidly than drugs can be developed, new drugs are usually outpaced by the organisms themselves.

"The usual course for a normal drug development that goes from the laboratory bench through animals to humans and eventually to the prescriber is somewhere in the area of eight to 10 years," Rybak says. "There are plenty of drugs in development, but by the time they get to the prescriber so that they can be used on a widespread basis, it may be too late for many patients. There are a few that are pending FDA approval, but I wouldn't say that they're the magic bullet. Drugs in themselves will never be the cure-all type of therapy we're looking for because they are only an adjunct."

Nevertheless, Rybak is looking forward to one drug pending FDA approval. The drug, called Synercid, will

be marketed by Rhone-Poulenc-Rorer. "We've done quite a bit of research with this drug, both in patients and in the laboratory, and for a number of those resistant organisms, it's going to be a very useful product," Rybak says.

Synercid initially will be available only for intravenous use, which will effectively restrict its use to the hospitalized infected community. In the future, there may be oral equivalents manufactured. According to Rybak, there is an oral product that has been in use for 25 years in Europe with an action that is somewhat analogous to Synercid, though Synercid has a minimum of two antibiotics in it and the European drug has only one. Resistance to that drug occurs more frequently than it would to two antibiotics.

Rybak says Synercid "will be a very welcomed addition to what we currently have in the face of gram-positive organisms, of which we are more fearful at the moment.

"Antibiotics are adjunctive to your immune system," Rybak observes. "People who come down with the most resistant kinds of organisms are usually quite debilitated, which increases the problem. If you combine [strengthening] the patient's immune system, antibiotics, and good infection control practices, you really have a powerful type of therapy, but if you try to use only drugs you're only going at one avenue of it. The spread of resistance is related to hospital personnel and the practice of medicine itself. Isolation of patients, hand washing, and so on are actually the most important tools. Unless you control the thread of resistance patient to patient, you run out of antibiotics too quickly because you can't develop them fast enough."

The resistant organisms are coming from patients outside the hospital as well as patients in it. Patients put tremendous pressure on physicians to prescribe antibiotics for conditions that otherwise would resolve themselves. Prescribers in the community now have a much larger array of antibiotics than they've never had before. "Typically," Rybak says, "in the past the most powerful antibiotics would be prescribed only in a hospital. Patients with moderate to serious infections would normally be hospitalized. Now, many of these people are treated on the outside because community clinicians have such a powerful array of antimicrobials available to them."

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Opinions vary on the bioethics of bioengineered skin

A seeming medical miracle is not without detractors

Reports of seemingly miraculous results from applications of bioengineered skin accrue almost daily since its approval by the Food and Drug Administration last May. Recently, an 8-week-old baby born with Dowling-Meara, a potentially fatal skin disease, became the first newborn to be treated with applications of Apligraf.

Because the infant might have died without the treatment, opposition to use of the material may be difficult for proponents to understand. However, some groups oppose bioengineered skin because the product is made from cells derived from neonatal foreskins, and they view circumcision as child abuse.

Jonathan Moreno, PhD, Kornfeld professor of biomedical ethics and director of the Center for Biomedical Ethics at the University of Virginia in Charlottesville, addresses the issue this way:

'Incipient life' issue not implicated

"One question is similar to the linkage issue between stem cell tissue and abortion. Does an innovative research field with potentially major implications for clinical care get morally underlined in connection with another practice with which many people have serious moral difficulties? [Stem cell research is] a much tougher case because in the case of abortion, the central issue is the status of incipient life. In the case of procedures that might use materials derived from circumcision, there is no issue of another incipient life. So at least one problem, the so-called 'innocent third party,' is out of the picture.

"With the linkage problem, you need evidence. Is there evidence this would cause more circumcisions? I don't see any reason to think that this is going to cause more people to have their male children circumcised. Secondly, we might be in a position in which an immortal cell line could be created at some point so that it wouldn't be necessary to use new material. I would hope that the people who are working on this would try to move us in that direction as quickly as possible in order to eliminate this issue."

Moreno adds that even if bioengineered skin production "didn't discourage circumcision, and even if we couldn't create cell lines within a short period of

time, then we move to the other question, which is, 'Is this practice so heinous that we shouldn't do anything at all that could even symbolically be seen to sanction it?' The anti-circumcision people argue that there is no evidence there are any health benefits to circumcision. It may not be possible to argue that cancer rates are reduced by the absence of the foreskin, but it is very much harder to argue that infections are not reduced."

"You can't assume the parents are going to have no moral interest in the tissue, so there's going to have to be some kind of consent procedure."

Some anti-circumcision groups have tried to move bioengineered skin production into the genital mutilation arena. "I don't think you can make a case that male circumcision is analogous to female genital mutilation," says Moreno. "The only reasonable argument the anti-circumcision people have is that this is a procedure that causes pain to the child. Given that the pain, so far as we know, doesn't cause any permanent damage to the child, and that there are ways to ameliorate the pain, and considering the deep feeling that some social groups have [about the cultural need for circumcision], I don't think that the argument against circumcision quite gets over the threshold that they need to get over. Of course, some religious groups may object to the use of their children's tissues for research purposes because they regard this tissue as something that has to be dealt with in a ritual fashion. You can't assume the parents are going to have no moral interest in the tissue, so there's going to have to be some kind of consent procedure."

Practical uses outweigh metaphorical ones

Rabbi **Elliot Dorff**, rector and professor of philosophy at the University of Judaism in Los Angeles, vice chairman of the Committee on Jewish Law and Standards of the Conservative Movement, and author of *Matters of Life and Death: A Jewish Approach to Modern Medical Ethics*, says, "Before we had the ability to use the foreskin medically, traditionally it was planted in the garden along with a seed. The idea was, 'May he grow and be fruitful.' The skin itself has no status in Jewish law. It's not a living organ or organism. If you can use it for saving someone's life, that's a very good use for it. If foreskins can be used in this way, then I would say even that it would be a positive obligation on our part to donate foreskins from circumcisions for this purpose rather than to use them in the rather metaphoric way of burying them."

M. Gregg Bloche, MD, JD, of the Georgetown/Johns Hopkins University Program in Law and Public Health in Washington, DC, touched on the consent issue in a recent article in the *Journal of the American Medical Association*: "Mainstream bioethics theory, that invoked by courts and government commissions, has yet to make a place for these underlying moral judgements. Instead, leading bioethics authorities tend to present the question of whether a person has consented autonomously to something as an empirical inquiry. . . . The law of informed consent, for example, has empowered patients in therapeutic settings."[1]

'Valid consent' vs. 'informed consent'

Kenneth W. Goodman, PhD, director of the University of Miami's Bioethics Program, says he feels strongly that to be valid, such consent needs to encompass much more than the phrase "informed consent" conveys. "You could inform someone of what you were going to do, and if you did it in a threatening way, their 'consent' would be invalid." Goodman prefers the term "valid consent," meaning that consent must, in addition to being informed, also be voluntary and given by people who have the mental capacity to give it.

"It's customary to allow parents to make all sorts of decisions for their children, and certainly for their infant children," Goodman points out. "Nevertheless, it's the sort of thing you want to make sure they give their permission to if it involves research or clinical use. Perhaps 20 or 30 years from now, we will no longer need that source of tissue. One of the things we do with any kind of research on tissue or cells is make clear to people that they're not going to share in any profits that the university or the corporation makes."

Harold Y. Vanderpool, MD, professor in the history and philosophy of medicine, Institute for the Medical Humanities, University of Texas Medical Branch at Galveston, had an eye-opening experience on the strong emotions surrounding circumcision. "At one point here at the University of Texas Medical Branch, I thought that we should have a rounds on that in family medicine. I thought it would be a slam-dunk in terms of everyone being able to talk about it in a rational fashion, to get the latest medical information and to talk about patient management and so on. Well, I had not seen a cat fight in medical ethics that matched that discussion!

"I assume if one could be able to bioengineer skin in some other way, that would be preferable, but at the same time, I think that the opposition position that assumes that circumcision is child abuse is certainly a minority one and would not be accepted by perhaps the majority of American citizens," Vanderpool adds.

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Product efficacy: Evaluating the evidence

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Products for wound prevention and treatment are more abundant — and, perhaps, more redundant — than ever before.

For example, the *Ostomy Wound Management* Buyer's Guide issue for 1998 lists 22 film dressings, 22 alginate dressings, 42 hydrocolloid dressings, 42 seating surfaces, and 62 nonpowered mattresses. Health care providers are exposed to new products at professional meetings, in newsletters and journals, on the Internet, by a colleague, or by a manufacturer's sales representative. This multitude of products vies for attention with clever advertising campaigns, T-shirts, buttons, and even plush toys.

But stuffed animals aside, how do you determine if you should use the new product? You need data. The manufacturers know the trinkets only get your attention for a moment, and in that moment they have to give you their best evidence of clinical efficacy in a pertinent patient population. So you walk away not only with a stuffed animal but with a few pounds of paper, too. In order to wade through that paper, or even stroll down the aisles of a poster session, you need to know a thing or two about clinical research, the various forms it can take, and how the results stand up to scrutiny.

Clinical studies fall into two broad categories: those that are simply observational or descriptive, and those that are experimental or comparative. Another way to refer to these two categories is uncontrolled and controlled, respectively. Within each of the two categories, there are subcategories, each with its own set of pluses and minuses. With any clinical study type, there are two major types of mistakes or error that can be made: random error or non-random error.

Random error has been defined as the difference between the estimated effect of a treatment and the true effect of the treatment (if it were known) that is due only to chance (Margolis, 1998). The magnitude of this type of error is often expressed as a p-value. Non-random error (also called bias) has been defined as the difference between the observed effect of a treatment and the true effect that is due to a systematic flaw. The most common areas of bias or systematic flaws in clinical studies are in patient selection, data collection, or overlooking a variable that could have a confusing effect on the study. Let's briefly discuss some of the more commonly encountered types of clinical research in wound healing and their potential for error or bias:

• **Case study or case series.**

This type of descriptive study usually looks at a single treatment in a single patient or series of patients. They are uncontrolled, meaning they are not comparing one treatment to another directly. Case studies are popular because they are quick to do and make a great poster. A case study or series may get your interest because everyone wants to see how a product performs in a human patient as opposed to an animal or cells in a petri dish, but it cannot establish efficacy of a product. One reason why is the placebo effect.

A placebo is an inert substance used as a control in some experiments. The placebo effect is the measurable or observable effect on a person or group that has been given a placebo rather than an active substance. H. K. Beecher evaluated more than two dozen studies and calculated that 32.5%, or about one-third, of those in the studies improved due to the placebo effect (Beecher, 1955). Other studies calculate the placebo effect as being even greater than Beecher claimed. The placebo effect and its potential magnitude should make it evident that the use of uncontrolled studies to infer the effectiveness of any treatment, therapy, or program should be taken with a grain of salt. A controlled study must be done to determine whether any improvement is actually due to the treatment rather than the placebo effect or some other variable.

Many who have done clinical research have noted that the process of being in a study can affect patient compliance, as well as engaging the other participants

to be more aware and engaged in overall care. One thing that case studies can do is stimulate ideas or garner interest for a more rigorous trial.

• **Cross-sectional studies.**

Also referred to as prevalence studies, cross-sectional studies are descriptive or observational studies that examine treatment status or outcome at one specific point in time. Prevalence studies often are done to determine an initial state prior to and after an intervention. A common example is when facilities do a pressure ulcer prevalence study prior to instituting a new type of support surface, wound care algorithm, or skin care products. After a period of time, they repeat the study to determine any change in in-house pressure ulcer development or prevalence. A change in outcome may be due to the intervention, but it is difficult to rigorously prove a temporal relationship between intervention and outcome. Cross-sectional studies are not sufficient to establish treatment efficacy.

• **Case-control studies.**

Case-control studies also are called retrospective studies. In this type of research, the treatment history and outcomes of a group of subjects with the condition of interest (cases) are compared to that of a group of subjects without the condition (controls). For example, patients with healed wounds or wounds treated with a new type of dressing are compared to those with non-healed wounds or wounds treated with a standard type of dressing. Patient group selection bias is a potential flaw in this type of study, so selection parameters must be carefully defined and matched for both cases and controls. Individual patient selection for treatment is another source of bias and can rarely be corrected since it is usually not known in a retrospective review. Information bias also is possible because the retrospective review of information may reveal poor documentation practices or inconsistencies in measuring or recording data. Retrospective studies are not often used to establish treatment efficacy, but have been used to supply evidence for rare outcomes (e.g., retrospective reviews of incidence of wound infection under occlusion) or outcomes that occur over long periods of time.

• **Randomized controlled trials.**

The randomized controlled trial (RCT) is often considered the gold standard for clinical research. The salient features of the RCT are that it is comparative (i.e., includes a control or placebo) and the patient selection method is not biased by the investigator because it is randomized by some method other than human decision. However, the RCT is not always the most appropriate or feasible type of study for determining a particular outcome. For example, if you want to know about risk factors, a case-control study may be a better design. If you want to know something about prevalence or the accuracy of a particular diagnostic test, then a cross-sectional study may be better. It also is possible to run into ethical issues in performing a RCT.

The fact that a study is randomized and controlled does not necessarily mean it is a great study. The method of randomization is a very important factor. Randomization of patients is critical to balance any unknown and therefore unaccounted-for factors that could influence outcomes. It is important for every patient in the study to have an equal chance of being assigned to the treatment or control group. The best randomization method is one that uses a mathematical technique such as a random numbers table to assign patients. When methods such as days of the week, medical record numbers, or a coin toss are used to assign patients to test or control, the study is not considered truly randomized.

Ensure evaluator of outcomes is 'blinded'

RCTs usually are blinded or double-blinded. Some studies are straightforward to blind. A pill or cream or gel may either contain active ingredients or not. Electrical stimulation may have current flowing or not. In dressing studies, it often is difficult or impossible to blind either the patient or the investigator to the identity of the test dressing vs. the control dressing. For instance, a piece of gauze looks quite different from a foam or film. In this case, it is important that the person who evaluates the wounds (i.e., measures them or rates them in some way) be blinded to the treatment by only being brought in after the dressings have been removed.

This is not an exhaustive discussion of the types of clinical research possible, but the objective has been to touch on the most common studies in the wound-healing literature and to point out some differences. In general, an observational (uncontrolled) type of study generates information but cannot be taken as strong evidence of comparative efficacy. A controlled study is a bit more rigorous and minimizes the placebo effect, but random patient assignment and blinding of the evaluators are vital to balance sources of bias.

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Skin cancer and Medicare: Reducing cost can be costly to patients

Medicare begins denying reimbursement

A recent study says a Medicare policy designed to reduce the cost of treating a kind of skin lesion called actinic keratosis goes against good medical practice and increases patients' risk of developing potentially fatal squamous cell carcinoma. Also, patients may well suffer adverse reactions to the topical treatment Medicare wants physicians to use for the condition. The study also evaluated how doctors treated other skin conditions for which minor surgery or other procedures are used.

To reduce its expenditures, Medicare has recently been making it more difficult for patients to receive some medical procedures by denying their physicians reimbursement. Removal of actinic keratoses during the patient's first visit with liquid nitrogen, a surgical code, is now one of those procedures in some states. The policy is intended to lower the incidence of unnecessary procedures.

Steve Feldman, MD, associate professor of dermatology and director of the Westwood Squibb Center for Dermatology Research at Wake Forest University School of Medicine in Winston-Salem, NC, and others reported in the *Journal of the American Academy of Dermatology*[1] that the majority of dermatologists choose to treat precancerous lesions by removing them on the patient's first visit. In some states, Medicare will not reimburse physicians who remove lesions on the initial visit. **Alan Fleischer**, a co-author of the Westwood Squibb Center study, says though Medicare is not technically prohibiting doctors from removing lesions during the initial visit, it is usually not reimbursing doctors for doing so.

Researchers analyzed all initial visits for actinic keratoses in 1993-94. Though some doctors in the Feldman study used topical treatment in conjunction with surgical removal of the lesions, none elected to use the topical treatment alone.

Ken Gross, MD, clinical professor of dermatology at the University of California at San Diego, says while Medicare's policy may be of some help to its pocketbook in the short run, in the long term it's going to cost the government more money — and patients their health — because many of the patients who receive only topical treatment will develop squamous cell cancer. "One of the great advances in dermatologic care was the use of liquid nitrogen for removal of actinic keratoses, which are basically pre-cancerous lesions. By simply freezing these lesions with liquid nitrogen, the cure rate is in the high 90s."

Gross says Medicare "wants doctors to treat with 5-f.u. [fluorocil] cream, an antimetabolite that was serendipitously discovered because people who were put on this particular antimetabolite as chemotherapy suddenly began to clear their skin precancers." The antimetabolite was put into a cream formula, marketed under the name of Efudex, and appeared to work fairly well.

However, Gross says, "My experience over the years has been that many of these patients will recur within a relatively short time after 5-f.u.treatment. The treatment itself is quite difficult; the patients can be very uncomfortable and experience quite a bit of reaction." Gross does not use Efudex for actinic keratosis treatment in general, reserving the cream as an intense postoperative treatment for the surrounding skin following squamous cell tumor removal. "It's well known that the cure rate for primary basal cell cancer of the skin with Mohs surgery is somewhat over 99%, but the cure rate for squamous cell is about 4% less. I think that the reason is that there are a lot of actinic keratoses, a lot of sun damage precancer, around the tumor. So, I use a very intense course of 5-f.u. around that area, and I can get away with it because it's a small area."

In particularly sunny areas, 5-f.u. causes a more intense reaction, including increased irritation, scaling, itching, and inflammation because of greater exposure to sunlight. It takes four to six weeks to adequately treat patients with 5-f.u., and another three weeks for them to heal. The sunnier states like Florida, New Mexico, and Texas (in all of which Medicare has instituted this policy) have more actinic keratoses, so it naturally costs more money to treat them there.

According to Gross, the cancers that develop in actinic keratoses have a lessened tendency to metastasize to other parts of the body than do squamous cell tumors of the lips or mucosa. "If people stop treating actinic keratoses," says Gross, "we're going to see an upswing in the number of squamous cell cancers, which is going to end up costing the government more money than treating the actinic keratoses would have. It seems illogical to me that you would allow a lesion that's a precancer and has close to a 100% cure rate to continue, or force people to use a suboptimal treatment."

Reference

1. Feldman SR, Fleischer AB Jr., Williford PM, Jorizzo JL. Destructive procedures are the standard of care for treatment of actinic keratoses. *J Am Acad Dermatol* 1999; 40:43-47. ■

NEWS BRIEFS

Company manages details, cost of catastrophic care

Burns and other catastrophic injuries have proved difficult to manage in the past, as their infrequent nature gives health care providers little experience in managing these events. The complications and costs of catastrophic care can skyrocket.

Now a company based in Lynnwood, WA, Avandel Healthcare, has created an innovative way to care for burns and other catastrophic injuries. According to Avandel representative **Laurie Lord Hambrecht**, RN, BSN, the company provides a clinical approach to burn care by creating outcome plans based on best-of-medicine protocols, and oversees the care of those cases as directed by the guidelines of its management program. As catastrophe manager, the company networks with centers of excellence to coordinate overall planning and care delivery with state-of-the-art partners. Hambrecht says Avandel's approach creates a tighter link between the clinical and financial aspects of burns and other catastrophes.

More information is available directly from Avandel Healthcare, 3400 188th St. SW, Ste. 570, Lynnwood, WA 98027. Telephone: (888) 478-6300. Web site: www.avandel.com. ▼

Silicone sheets painlessly reduce pediatric scarring

Most children are incorrigibly curious and love an adventure. Unfortunately, incautious children often put themselves at risk of injury from accidents — and the scars that accident wounds can leave behind. Parents and caregivers will be glad to know scarring can be kept to a minimum using pure silicone sheeting now available at the local pharmacy.

Once available only by prescription or in hospitals and burn centers, these thin, pliable sheets, named ReJuveness Pure Silicone Sheeting, can be applied to a wound once it has closed. "Since it is painless and has no side effects, it makes it perfect for use on children," says **Laurie J. Polis**, MD, director of the Soho Skin and Laser Dermatology Group in New York City and advisor to ReJuveness.

ReJuveness may eliminate or reduce the need for painful and expensive surgeries or injections to minimize scars. "In many cases, doctors and their patients felt that the scar reduction procedure was worse than living with the scar itself," Polis says. "Unless a scar is completely obvious, such as on the face, or physically uncomfortable, I don't think I would recommend these invasive procedures for a child." She says the best bet is to try silicone sheeting first.

Electrostatic field may be active principle

While no one knows exactly how silicone sheeting helps reduce scars, the prevailing scientific belief is that an electrostatic field forms between the sheet and the surface area of the skin. Over a period of time, ranging from several weeks to months, the electrostatic field helps lighten, flatten, and smooth the scar painlessly and without side effects. According to Polis, "At no time is any silicone ever released into the skin from the sheet."

Of the 62 million new scars formed each year in America, about 9 million are considered either hypertrophic or keloid. Hypertrophic scars are red and raised within the wound site, while keloids are red, raised, and expanded beyond the wound site. While these scars, which result from abnormal healing, can affect anyone, they're more common among those with darker skin tones, such as African-Americans and Asian-Americans. Family history of these types of scars can also play a role, and hormones — such as the fluctuations that occur during puberty — may be implicated as well.

Paul Striker, MD, attending plastic surgeon at the New York Eye and Ear Infirmary and at the Center for Specialty Care in New York City, uses Rejuveness extensively, and has this to say about the product: "I've found it extremely efficacious in reversing heavy scarring. It's cost-effective, there's no risk, and it avoids a surgical correction. Very often, when someone's had a cut on the leg or the face that would traditionally require a surgical correction or painful injections of cortisone, I've been able to get that scar flattened and the coloration improved by just the application of the silicone sheeting at home. I've been universally successful if my patient complies."

Striker does a lot of eyelid surgery and laser resurfacing in his practice. "If I see that scar starting to get

a little reactive, I immediately apply the Rejuveness," he says. "I don't have the scientific studies to prove that it's preventing scarring, but my professional opinion is it's very helpful. The nice thing about this is there's no 'bottom line.' The worst you can get is a little rash from sweating, and then you stop for a day or two. With surgery, you can get infection or failure or complications, and cortisone injections are painful."

This is good news for parents who would like to reduce unsightly scars on their children for any number of reasons: the scar brings back bad memories, makes the child feel self-conscious, restricts movement, or is easily irritated and itchy. Polis emphasizes that immediate care for a wound is imperative to prevent foreign-body contamination and infection. Equally important are getting sutures if necessary, and avoiding plastic surgery, ear piercing, and tattoos if there is a history of this type of hypertrophic or keloid scarring.

For more information about the product and problem scarring, check out the company's Web site at www.rejuveness.com. ▼

Curative, Novartis create educational program

Curative Health Services and Novartis Pharmaceuticals are collaborating on an educational program to give Curative's Network Wound Care Center medical and clinical associates the latest clinical and research information on Apligraf, Novartis' bilayered living skin equivalent.

Apligraf was approved by the Food and Drug Administration last May for treatment of venous leg ulcers, which affect between 600,000 and 1 million people in the United States, more than 90% of whom are over age 50. The product, which is flexible and functions much as natural skin layers do, was shown in clinical trials to heal even longstanding venous leg ulcers (wounds in existence for more than a year) more effectively and faster than compression therapy alone, as reported in the *Archives of Dermatology*.[1]

Curative is capturing and tracking outcomes data on Wound Care Center patients treated with Apligraf. "Apligraf looks promising for specific patient groups and provides another option to be considered in developing a treatment plan for each individual patient. However, long-term effectiveness will need to be established," says **John Vakoutis**, Curative's president and CEO.

Curative, a disease management company in the treatment of chronic wounds, manages more than 150 Wound Care Centers nationwide. The company also provides services to health care providers through a nationwide network of wound care programs that offer interdisciplinary wound care. Headquartered in Basel, Switzerland, Novartis and its affiliates own exclusive worldwide marketing rights to Apligraf, which was developed and is manufactured by Organogenesis in Canton, MA.

For further information, contact Curative Health Services, 150 Motor Parkway, Hauppauge, NY 11788. Telephone: (516) 232-7000.

Reference

1. Falanga V, et al. Rapid healing of venous ulcers and lack of clinical rejection with an allogenic cultured human skin equivalent. *Arch Dermatol* 1998; 134:293-300. ■

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The Wound Calendar

• The 1999 Symposium on Advanced Wound Care and Medical Research Forum will be held April 24-27 in Anaheim, CA. For information, call (800) 237-7285 ext. 200, or (610) 688-8220 ext. 200.

• The 1999 Centers for Disease Control and Prevention Diabetes Translation Conference will be held April 26-29 in Albuquerque, NM. For information, call (770) 488-5505.

• A workshop on practical experience in suturing techniques and using tissue adhesives and the treatment of acute and chronic wound problems will be held May 19-22 in San Diego. For information, call (619) 467-9010. This workshop will be repeated Oct. 13-16.

• The American Academy of Physician Assistants Annual Conference will be held May 29-June 3 in Atlanta. For information, call (703) 836-2272.

• The 36th North American Federation Congress of the International College of Surgeons, United States Section, will be held June 23-27 in Cancun, Mexico. For information, call (312) 642-3555.

• The annual conference of the Wound Ostomy and Continence Nurses Society (WOCN) will be held June 20-24 in Minneapolis.

The conference will be preceded by a day-long preconference session organized by the Wound Healing Society. The four-part session, titled "Therapeutic Possibilities for Problem Wounds," will focus on defining a problem wound, cell implantation, gene therapy, and physiochemical modalities. Attendees also will have an opportunity to improve their computer database management skills. For a copy of the full conference agenda, visit the WOCN Web site at www.wocn.org or call the WOCN national office at (888) 224-9626.

If you have a conference, seminar, or other wound care-related event you would like listed in the calendar, please send the information to: Wound Care, *P.O. Box 740056, Atlanta, GA 30374.* ■

Coming in Future Issues

■ Evidence-based medicine: Centers of excellence in the UK
■ Medical imaging and telemedicine
■ Update on light therapy: Does it really speed wound healing?
■ Enzymatic wound debridement: A new in vitro method uses porcine skin and muscle tissue

CE objectives

After reading each issue of *Wound Care*, the health care provider will be able to:

• identify management, clinical, education, and financial issues relevant to wound care;

• describe how those issues affect wound care providers and patients;

• describe practical ways to solve problems commonly encountered by care providers in their daily activities. ■