THE DEVELOPMENT OF TOPICAL THERAPY

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In the preparation of such a presidential address it was my initial impression that a suitable subject for presentation would be readily available from out of the great volume of material produced over the past several decades on the subject of thermal injury. However, as the search continued, and as the deadline approached and the intensity of the search grew to an almost fever pitch, it became obvious that the appropriate topic was as elusive as a really acceptable and effective topical agent for use in the care of the burn wound. This analogy provided a welcome solution to the quest, and it was decided to present to you a résumé of the development of effective topical therapy as we know it today.

I thought this might be of particular interest to those who have entered the burn field in the past 5 or 6 years and have not had the dubious honor of experiencing the great problems attendant upon the care of the thermally injured prior to that time. To those who earned their spurs in the days when things were not so pleasant, possibly the recounting of old experiences will recall enough fond memories to justify your indulgence in my reminiscing.

Ancient writings contain references to many medicaments advocated for the topical application to the burn wound. The early Egyptians utilized oily strips of linen; the fifth and sixth century Chinese used the extract of tea leaves; and the old Jewish cultures in the Middle East used ink derived from a variety of sources. Hippocrates’ advocacy of the use of “old swine’s scum” (fat), persisted for centuries, and was perpetuated in the recommendations for burn treatment as recommended by Theophrastus Bombastus Von Hoenheim, writing under the pseudonym of Paracelsus as follows:

“It consisted of the fat of very old wild hogs and bears, heated half an hour in red wine, then dropped into cold water, which was next skimmed and the fat rubbed up with roasted angleworms and moss from the skull of a person hung, scraped off during the increase of the moon, to which were added bloodstones, the dried brain of a wild hog, red sandalwood and a portion of a genuine mummy.”

Ignorance, superstition and tradition resulted in the concoction of some rather weird combinations of substances which, when applied to the burn surface, were believed to hasten the healing and combat the “toxemia.” That some were soothing to the victim was a happy circumstance.

In the seventh century Paulhus of Aegina recommended the following:

“A whole raw egg immediately applied upon soft wool is advocated as it cools moderately and dries without being a stimulant... Put pigeon’s dung into a rag of linen, burn it and mix the ashes with oil and use.”

Each particular remedy had its own fierce proponents, but evidence pro and con was rarely available in anything other than a testimonial. The tremendous variety of treatments advocated with no real information on which to base an intelligent decision led Adam MacDougall to remark in 1819 that “it would equally exceed the bounds of convenience and utility, to particularize all the remedies that have been recommended in the treatment of accidents of this kind.” It was evident that the large number of remedies proposed were an accurate testimonial to the ineffectiveness of any one of them. Nevertheless the search for something to hasten the healing of the burn wound continued, and physicians began to look more closely at the wound itself and the cause of the problems that it generated.

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One of the most popular applications was that which came to be known as "Carron Oil." This oily substance was equal parts linseed oil and lime water, and obtained its name from the Carron Iron Works of Stirling, Scotland. The exact origin of the medication is unknown, but it was apparently developed about the time of the establishment of the Iron Works near Edinburgh in 1759. It was initially advocated for use in industrial burns because of its slight analgesic power, but was rapidly adopted for the general treatment of thermal injury. That it continued to be used for over two centuries is evidenced by an article in Lancet of 1895 by Inspector General Smart as follows:

"The local treatment to all the cases in the first stage of depression and of inflammation was by Carron Oil on cotton wadding; in the second stage of supplicative action...by Oxide of Zinc Powder and by Calomine Ointment; and in the granulating and cicatrizating stages by the same as in the supplicative; but when the granulations became pale and flabby by strips of lint covered with resinous ointment containing an excess of turpentine."

In 1848 James Syme, then professor of surgery at the University of Edinburgh, plagued by septicemia and erysipelas among the burn population in his hospital, moved some of the patients into a separate building known as "The Janitor's House," which later became a burn hospital. This lessened the danger to the remainder of the hospital population, but did little to alleviate the problem for the burned patients. Three decades later in 1875, Syme's son-in-law, Joseph Lister, published in Lancet an article in which he advocated the use of boric lint and carbolic acid as the local treatment for the burn wound. This was rapidly adopted by many and continued to be popular for several decades, but was finally abandoned because of phenol intoxication and the inability of the carbolic spray to control the burn wound infection unless the concentration was strong enough to devitalize tissues.

In the early twentieth century Barthe de Saundfort introduced a medicated paraffin called "Ambrine," the formula for which was kept secret but which was copied widely throughout the Western World. This was sprayed on at a temperature of 50°C, and the solidified covering was expected to exert pressure and protect the burn wound. The initial paraffin layer was followed with a covering of cotton wool, then a second layer of the paraffin, and this in turn followed by another layer of wool. Dressings were changed daily or less frequently as dictated by the appearance of the local wound, but the technique was abandoned because of the laborious effort required for its use and the subsequent development of easier and more effective techniques. A closely meshed net dressing impregnated with soft paraffin, balsam of Peru, and olive oil, and known as "Tulle Gras," became quite popular in France and England shortly afterward, and is still widely used as a dressing material in those regions today. The addition of topical anesthetic agents to the dressing is a common practice. While cod liver oil was introduced by Lohr in 1935 and was claimed to be bacteriostatic and stimulate the growth of new epithelium, it has never gained any wide popularity and is rarely used today.

Picric acid appeared as a treatment of the burn wound shortly after the turn of the century, and became initially quite popular. Often carried in an oil and alcohol vehicle which made it much more soluble, it was soon abandoned because of its poisonous properties manifested by toxic symptoms referable to the gastrointestinal, genitourinary, circulatory, or central nervous systems, or all in combination. It was rapidly supplanted by tannic acid, but is still available in many drugstores as Butesin® Picrate for the use of small minor burns.

In 1925 Dr. Edward Clark Davidson of the Henry Ford Hospital introduced the use of tannic acid in the treatment of burns with the following statement: "The clinical and experimental facts suggest that the rational manner of combating the toxemia would then lie in some form of local treatment which would prevent the absorption of products of protein decomposition." He had worked initially with phosphotungstic acid, but was informed by a colleague that tannic acid was a similar strong protein precipitator and decided to use the latter. The tannic acid had a much more pronounced coagulant effect than did the previously used picric acid, and the toxic symptoms were not as immediately or as frequently observed. In the treatment of the wound the burned area was covered with dry sterile gauze pads which were held in
place by sterile gauze bandages. This dressing was then soaked with a 2.5% aqueous solution of tannic acid. These wet dressings were continued until a hard coagulum formed, and then the open method of treatment of the burn wound was utilized. Some variations of the tannic acid method, instead of using wet dressings, called for tubbing or continued spraying.

The enthusiastic use of the tannic acid method continued for approximately 15 years, and although a publication in the British Journal of Surgery in 1937 described liver necrosis in burned patients treated with tannic acid, it did not correlate the liver necrosis with anything other than the burn injury itself. The fact that symptomatology did not ordinarily appear for 36 or more hours after the application of tannic acid led many clinicians to believe that the death of the patient was due to causes other than the tannic acid. It was not until 1942, when tannic acid was proved responsible for central lobular necrosis of the liver seen in patients treated with this substance, that it was abandoned as a method of treatment for the local burn wound. While it enjoyed widespread use for a time, it was not universally accepted. From one clinic in Austria the following is derived: "Tannic acid has been abandoned because in so many cases secretions collected under the eschar and gave rise to infection." This statement was prophetically true in emphasizing that the eschar produced by protein precipitation did nothing to protect the wound against bacterial infection and actually led to a false sense of security.

In 1935 Bettman of Portland, Oregon, in an attempt to hasten the tanning action of the tannic acid, added a 10% solution of silver nitrate to the 5% tannic acid. The silver nitrate application immediately followed the tannic acid, and the combination became quite popular because rapid tanning was accomplished in a matter of seconds, thus minimizing the nursing care. This appeared to be its only real advantage, but the combination medication remained quite popular until the tannic acid preparations were abandoned.

Thus infection continued to be the main problem, and none of the topical agents had successfully combated this major threat. It was not until 1933, when Aldrich published his classical article in the New England Journal of Medicine, that infection of the burn wound gained its proper perspective. Working with W. M. Fieror, he reviewed the toxemia theories of burns and discarded them. Aldrich explained his thesis as follows: "One is impressed with the fact that there is enough obvious infection present in the burn area to account for all symptoms and physical signs." His bacteriological studies confirmed this thesis. The two investigators felt that infection was the best bet to explain the "toxemia" and began a search for substances which would combat the infection. The aniline dyes were coming into use in medicine and a trial with one of them was felt justified. Aldrich's article reported the results using 1% gentian violet spray applied immediately upon admission and reapplied every 2 hr until a firm eschar was formed. After this the spray was repeated every 4 to 6 hr. He mistakenly stated that "the burn is thereby sealed steriley under an impermeable cover." While he was making a tremendous advance with an antibacterial agent, he was falling into the same trap as others had previously in believing that the eschar which he was forming by protein precipitation would protect the wound indefinitely.

It soon became obvious that infection was continuing in patients treated with gentian violet, although the streptococcal infections which had been such a plague in the burn wards were reduced. In an effort to increase the spectrum of activity to include Gram-negative organisms, the "triple dyes" comprised of gentian violet, brilliant green, and acriflavine were also introduced by Aldrich. Although these appeared more effective in the test tube, the Gram-negative organisms were no more effectively controlled in the burn wound. But progress was being made in the search for an effective topical agent, only to lose momentum in favor of other methods.

With the publication by Harvey Allen in 1942 of the occlusive dressing method of the care of burn wounds, much of the impetus for the use of topical agents in the therapy of the local burn wound was lost. Allen showed that thorough cleansing, debridement, and the use of lightly impregnated Vaseline® gauze with occlusive dressings reduced his mortality rate to almost one-fourth of what it had been with tannic acid or with tannic acid and silver nitrate. He summarized his feeling as follows: "It is not logical nor wise to substitute for a safe and tested method an elaborate time-consuming procedure which involves the use of powerful chemicals concerning whose possibilities for harm we are
still in doubt.” Thus were laid to rest, at least temporarily, the chemical escharotics. This opinion was further bolstered by the experience of Oliver Cope in his report in the *Annals of Surgery* in 1943, in which he described the success in 39 patients treated as a result of the Coconut Grove fire. Both of these surgeons were echoing the sentiments Frank P. Underhill voiced in 1930, when he remarked parenthetically in his monumental treatise documenting the fluid shifts following thermal injury that he could not understand: “Why (should one) stop drainage by application of substances like trinitrophenol or tannic acid? Why not treat a burn like any other wound?”

With the appearance of sulfonamide drugs on the medical scene and their brilliant success in the control of the streptococcus and some of the other Gram-positive bacteria, one could predict that it was not long before the substances were used topically on the burn wound. Sulfanilamide, sulfa diazine, and sulfa thiazole as ointments and sprays were used following the publication by Pickrell in the *Johns Hopkins Bulletin* of 1941. The initial success was blunted by mounting reports of renal toxicity. With the advent of penicillin and the other antibiotic agents, the enthusiasm for topical sulfanamides in the treatment of the burn wound for some reason rapidly diminished and finally died out. This was unfortunate, for it was another 20 years before effective topical therapy really became a reality, and it was already within the grasp of the early workers in this area.

The amazing success of the systemically administered antibiotic agent in other types of infection pushed into the background the topical use of drugs for burn wounds, and little was to be heard of them for many years. Although they were habitually used under dressings, the systemic use was emphasized by most. However, the systemic use of large amounts of even newer antibacterial agents failed to surmount the problem of burn infection. This was due in great part to a lack of understanding of the source of sepsis in the burned patient population, and it was not until the identification of the burn wound itself as the primary focus that attention was again turned to topical agents. The classic work of Teplitz, followed in short span by that of Order, paved the way for the understanding that systemic agents would be ineffective in such a circumstance.

In 1965 Moyer, whom we honor with the Resident’s Research Award of this Association, and Monafo published reports of their results with the use of 0.5% silver nitrate solution in the topical treatment of the burn wound. Moyer had earlier presented his results at a meeting at New York Academy of Medicine, and these were greeted with some skepticism by his audience. Following the later publication, however, other investigators began to duplicate his results and share in his enthusiasm. At the Surgical Research Unit here in Fort Sam Houston, we knew the truth of his figures as they confirmed our own studies. Stimulated by the work of our co-investigators, Teplitz and Order, and aided by the suggestion of Lindsay that Sulfamylon® was effective against *Pseudomonas*, we began to investigate topical mafenide as an agent in 1962. Careful, painstaking, and exhaustive laboratory studies accomplished by Lindberg, Walker, Mason, et al., established what appeared to be the optimum dosage schedule and concentration. The time for patient trial was at hand, and fate as usual played an important role in the form of a young boy admitted 11 days postburn with advanced burn wound sepsis. Within 24 hr of the onset of topical therapy the obtunded child was alert, and by 48 hr exhibiting only a low grade fever, eating well, bright and happy. The next trial was in a freshly burned 2-year-old, but the decision was a difficult one. The burn was a well circumscribed, full-thickness injury of thighs and lower trunk readily amenable to primary excision, a procedure with which we were singularly successful in that age group. Should we forego what looked like sure success for a trial of what, even with the first apparent triumph, was an uncertain method? Topical therapy was elected. The results were immediate and startling, and the entire patient population was soon included in the study.

At the time of Moyer’s first presentation we had almost 200 patients, and although Dr. Moyer and I were usually in close touch, neither was aware of the results seen by the other. The study was closely controlled and later limited to a small number of investigators in order to be certain of the results and to preclude an overenthusiastic response. In the light of the success of the technique and the absence of any serious unknown problems appearing, it would seem that this close scrutiny was well justified. Other workers rapidly confirmed the success of the
topical mafenide in controlling burn wound sepsis, and the search for additional topical antibacterial agents was widened. Among the earliest to come later on the scene was gentamicin, which was designed specifically against the dominant pathogen Pseudomonas aeruginosa. Its unrestricted use in such instances has led to the development of resistant strains predominating in the hospital environment, and points up the inevitability of banking exclusively on a single agent. Other substances are still being investigated, including the silver sulfadiazine complex of Fox and the technique of sub-eschar installation of antibiotics as practiced so successfully by Baxter.

What has been the result of this progression from superstition and tradition through chemical escharotics to definitive substances aimed at a specific spectrum of bacteria responsible for burn wound sepsis? For those only recently come upon the scene it is difficult to appreciate the major transformation which has resulted in the burn wards and the burned population. Prior to effective topical therapy, the burn wards were known for their repelling odor, the fatigue duty, disconcerting frequency of fatal septic complications, and the often pungent smell of frequently used disinfectants. The patient population that survived the prohibitively high mortality rates were drawn and tired, wasted, hollow-cheeked and glassy-eyed, disinterested in surroundings, often disoriented, anorexic, and even under the best nursing conditions frequently inundated with gross infection and odor. The physicians and nursing personnel rapidly lost their initial enthusiasm, and often wore a haggard appearance legitimately earned through long, hard hours of frustrating efforts. Today the hospital visitor seeking the burn ward is no longer told to “follow his nose.” The wards themselves are clean, airy, and except under unusual circumstances free of odor. While many are quite ill, the majority of the patients remain alert; nutritional balance is much more readily attained; interest in the surroundings is normal, as is response to external stimuli; healing of partial-thickness wounds is accomplished with greater rapidity; and the surroundings as well as the attending personnel are cheerful.

This does not mean that the problem of burn wound infection is solved, but it does mean that a solution is possible. As we continue our efforts to understand the pathologic processes involved in the problems of burn infection, we will undoubtedly be able to define the problem in its precise limits and design the specific therapy appropriate for the occasion.

To those who preceded us we owe a debt of gratitude for their continuing efforts in the face of repeated failure. To those who follow us, let us say: Do not reduce your efforts! Continue the search! Your rewards will be great.

REFERENCES