

THE APPLICATION OF CARBAMIDE (UREA) THERAPY IN WOUND HEALING*

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RECENTLY, Reid¹ pointed out that "it is erroneous to give . . . the idea that the problem of wound healing is essentially synonymous with the principles of asepsis and antisepsis." He notes further, that "among the first of the great principles of wound healing to become established, was the importance of eliminating or preventing the formation of necrosis and débris in wounds." By the removal of dead tissues, bacterial growth is eliminated or reduced to a minimum. Christopher² likewise condemns the use of antiseptics in fresh open wounds, and lists the removal of foreign bodies and devitalized tissues as two of the most important underlying principles in the treatment of fresh wounds. It was the consideration of the importance of this factor which first led us to examine the usefulness of a strong carbamide* (urea) solution, which is a potent agent for dissolving protein substances, such as dead tissues, as a therapeutic agent in wound healing.⁴ This rediscovery of an agent, first used more than three decades ago,⁵ but since forgotten, has produced such good results that an unexpected interest as well as innumerable questions concerning the details of its application to wounds of various types have arisen. It has, therefore, seemed desirable to describe the application of carbamide (urea) in greater detail and to summarize two more years' experience with the product.

The virtues of carbamide have recently been well summarized by Mertins,⁶ essentially as follows:

(1) Carbamide in aqueous saturated solution, by its power of dissolving necrotic débris, removes the chief deterrent to healing in many types of chronic infection.

(2) It is almost totally nonirritating to living tissue.

(3) It is mildly bactericidal to many forms of organisms, especially those producing putrefaction.

(4) It almost immediately eradicates all odor without producing another odor.

(5) It is inexpensive.†

* We have adopted the suggestion of a recent reviewer,³ in electing to use the chemical term carbamide, because of the suggested association in the minds of some of the term urea with urine, and also because this substance is now prepared synthetically.

† We are indebted to Rare Chemicals, Inc., of Nepara Park, N. Y., for trial supplies of "eucupin" dihydrochloride.

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These good qualities, which are approximately the same as those which were pointed out in our initial report,¹ have been supported by all of the observations which we have made since that time. However, two problems have arisen in connection with the use of carbamide. One of these has to do with the physical nature of the material applied to the wound. When we first used carbamide it was applied either in a strong, usually saturated, aqueous solution or in the crystalline form depending on the degree of moistness of a wound. The solution was naturally the method of application of choice in any fistulous wound. Mertins has used it in the aural canal for the treatment of chronic otitis media. In many other areas, the solution could be employed, but we have generally preferred the crystals, when their application was possible. Their chief disadvantage is their tendency to dry out and cake on occasion, and the difficulty of maintaining them in proper contact with the tissue at times. To obviate these difficulties we have compounded a urea paste for occasional use, the preparation of which is described below.

The other problem which we recognized in our early work and which has become important enough to warrant an attempt to obviate it, is the pain which is incident to the use of carbamide in some cases. This is due to the fact that hypertonic solutions may be painful to denuded tissues. Of such origin, is the aggravated pain of an aching tooth when candy is dissolved in the mouth. After a trial of many local anesthetics, a product has been found which is not only effective in almost all cases, on mucosa as well as denuded areas, but also has a useful bactericidal action.⁷ This is iso-amyl-hydrocupreine, which is known as "eucupin." Although originally synthesized as a bactericidal substance, its high potency as a local anesthetic has made it even more useful.^{8, 9} The prolonged anesthesia which results has been particularly useful for our purpose. Since the free base is not water soluble, "eucupin" dihydrochloride is the compound ordinarily utilized. We have mixed this compound with the crystals of carbamide or added it to the solution in a concentration of 0.4-0.5 per cent. It may also be incorporated in the carbamide paste, which is composed of: Carbamide 50.0 per cent, karaya gum 2.5 per cent, eucupine 0.5 per cent, and is compounded as follows:

Five hundred Gm. of carbamide* (crystal urea, DuPont) are dissolved in approximately 300 cc. of hot water. Half of this solution is then placed in another container and 25 Gm. of powdered first grade gum karaya (India gum) are dissolved in it by vigorous stirring. The resulting paste is then sterilized by autoclaving. To the other portion of carbamide solution 5 Gm. of "eucupin" dihydrochloride are added and this mixed with the autoclaved carbamide-gum karaya solution, and made up to a final volume of 1,000 cc. This solution on cooling is ready for use.

It has been our practice to treat all infected and, occasionally, some rel-

* Carbamide may be purchased from most chemical houses. A very pure product, which may be obtained at low cost, in quantities of 100 pounds, is crystal urea, manufactured by E. I. DuPont de Nemours & Company, of Wilmington, Del.

actively fresh wounds containing dead tissue, until clean, with carbamide crystals, strong carbamide solutions or the paste. Whether or not the "eucupin" dihydrochloride is added depends upon the pain it causes in the wound, and the type of patient. When the wound is clean and granulating, epithelialization is often completed with other dressings. A word should be said concerning the type of granulation tissue which is obtained by employing carbamide therapy. It is far superior to that which results from the application of many antiseptics or occurs in the presence of infection. The carbamide granulation tissue is healthier and more highly vascularized. It is pink, flat, and ideal for skin grafting. The following cases are presented to demonstrate the principles of carbamide application.

ILLUSTRATIVE CASE REPORTS

Case 1.—No. 66256: J. W., male, age 37, entered Scripps Memorial Hospital December 30, 1936, with typical signs and symptoms of a lobar pneumonia of the right lower lobe. For the first twelve days, although acutely ill, the patient seemed to hold his own. On the twelfth day, his condition was definitely worse with rising temperature, and with clinical and roentgenologic evidence of pyopneumothorax. Aspiration at this time recovered 400 cc. of grayish, foul smelling pus, suggestive of lung abscess or anaerobic infection such as is occasionally found following the rupture of a superficial lung abscess into the pleural cavity. Because of the danger of a serious cellulitis of the chest wall with repeated aspiration, immediate open thoracotomy was performed. Under local anesthesia, the eighth rib was resected in the posterior axillary line for a distance of three inches. A large caliber, two-way rubber tube was fastened into the wound for irrigation and drainage. Following the evacuation of a large amount of foul pus, the cavity was irrigated with saturated carbamide solution which was repeated every four hours. There was no evidence of pleurobronchial fistula, but had there been, the use of urea would not have presented such a complication as does Dakin's solution in these cases, as it is not so irritating to the bronchial mucosa. The purulent drainage was deodorized within a few hours—a very helpful property of urea in all foul smelling infections. The clinical course from the time of the thoracotomy showed progressive improvement, the temperature gradually subsiding in two weeks' time, and the patient discharged home, ambulatory, in 21 days, the wound draining very little.

We feel that saturated carbamide solution is far superior to Dakin's solution as an irrigating fluid in empyemata. Its greater lytic properties are more efficient particularly in the anaerobic type of infections, such as detailed above, where control of the infection is directly dependent upon elimination of necrotic tissue on which the bacteria are dependent for their existence. Saturated carbamide solution may best be employed in intracavity infections such as empyemata, nasal sinuses and chronic otitis media; fistulous tracts, as in chronic osteomyelitis; postoperative rectal fistulectomy; ischiorectal abscess cavities; and in deeply infected wounds where the crystals cannot be effectively applied as in deep traumatic wounds and postoperative infected wounds such as the perineal wound following resection of the rectum.

The following case demonstrates the lytic action of carbamide in crystalline form. At no time did the patient complain of discomfort.

Case 2.—No. 9400: F. W., female, age 23, was admitted to the Scripps Memorial Hospital January 3, 1938, with a history of increasing pain and tenderness over the

sacral region for the preceding four days. Examination showed a healthy adult female whose clinical and laboratory findings were both normal other than the localized painful area. Inspection here revealed a large, tender, indurated, erythematous area. The infection seemed deep and there was no localization suggestive of a furuncle or carbuncle. An exploratory operation, January 5, 1938, demonstrated a large, thickened, infected pilonidal cyst, which was removed by careful dissection down to the posterior sacral attachments. The wound was packed with carbamide crystals and no attempt at closure made. Any remaining necrotic or inflammatory tissue was promptly removed by the carbamide, and the wound rapidly granulated up from the bottom and healed without complications. The tendency for recurrence due to leaving behind a portion of the cyst wall is well known. The use of carbamide with its strong, lytic action on devitalized tissue, is a great aid in cleaning up such a wound and keeping it clean for normal reparative processes and thus reducing the chance of recurrence.

Case 3 demonstrates the use of the carbamide "eucupin" water-soluble paste, necessitated by the pain resulting from application of the crystals.

Case 3.—M. G., female, received a third degree burn, November 16, 1937, involving the entire lateral surface of the left thigh from the knee joint to above the iliac crest extending anteriorly to the middle of Poupart's ligament and thence down the anterior surface of the thigh in this same line. The posterior surface of the thigh was involved for about an inch past the junction of the posterior with the lateral surface. This wide area had been treated with tannic acid in the usual manner, but subsequent infection of the burned surface had undermined the crust which had separated in some areas and from such denuded surfaces large amounts of purulent exudate were discharged. The patient had a septic fever with associated constitutional symptoms. On December 4, 1937, dry carbamide crystals were generously applied, and in less than a week's time the majority of the crust and underlying necrotic tissue had been removed. The carbamide crystals then became so painful that the carbamide paste with "eucupin" dihydrochloride was applied. This was well tolerated and very efficacious. Continued use of this paste for two weeks produced a very clean, healthy, granulating surface, ideal for skin grafting. Since the patient was unable to enter the hospital at this time treatment of the burned area was continued with an epithelializing agent and subsequent skin grafting was successful.

The following two cases are presented to illustrate the use of carbamide crystals in traumatic wounds and to demonstrate that the compound may often be applied without discomfort as well as to remove the fear that carbamide may have a deleterious effect on tendons. The blood supply of tendons is notably less than in many other tissues, but in our experience with a number of cases in which tendons were directly exposed to the action of carbamide, even in the presence of suturing and traumatization, we have seen no evidence of a harmful effect.

Case 4.—No. 9224: R. G., male, age 4, entered the hospital October 29, 1937, with the history that while playing in the street he was struck and run over by a heavy truck, sustaining a severe injury to the left foot. Physical examination revealed moderate shock as evidenced by pallor, rapid pulse and respirations. There was no evidence of injury other than to the left ankle except subcutaneous emphysema involving the left chest wall and the left side of the neck. Roentgenologic examination showed no evidence of fractured ribs and the laboratory findings were normal. The patient's condition improved after antishock measures were applied and the injured ankle was inspected under ethylene anesthesia. Over the anterior aspect of the left ankle joint the skin was absent as a result of a grinding force which had completely denuded an area two inches in

diameter. It appeared as if the foot had been placed on an emery wheel and a complete section of the soft tissues ground out, including skin, subcutaneous tissue, fascia cruris, sections of the tendons, extensor digitorum longus, hallucis longis and tibialis anticus, together with the dorsalis pedis artery and accompanying nerve, ligaments attached to the anterior surface of the talus and the entire articular surface of the talus. The roentgenogram showed the superior margin of the talus ground off so that the articular surface presented a straight line. Operation consisted of débridement of all obviously devitalized tissue. Skin edges were freed and dissected back with the aid of extending incisions above and below. Blood vessels were ligated and repair of the three extensor tendons carried out with lengthening due to loss of substance. The skin defect could not be entirely closed because of the marked tissue loss, but was approximated as well as possible and the foot immobilized at a right angle in a molded plaster splint. At the first dressing, three days later, there was considerable purulent discharge from the wound, and carbamide crystals were introduced generously. The foot was kept immobilized, with only the application of carbamide crystals at the time of the daily dressings. In six weeks the plaster splint was removed, and over the following two weeks gradual weight bearing was allowed with the aid of crutches. The wound was still draining slightly from a small central sinus but in eight weeks' time was entirely healed and the extensor tendons were functioning normally. A mild, acquired talipes valgus was corrected with a leather ankle and arch support, which gave a normally functioning foot.

In this case, as in many others, carbamide was employed without discomfort. In a child with a seriously contaminated, traumatic wound involving soft tissue, tendons, blood vessels, bone and joint surfaces with following infections, deterrents to wound healing were so satisfactorily controlled by the application of carbamide crystals that no injury to the tendon repair occurred, and no serious osteomyelitis developed, leaving an ankle joint without dysfunction. The following case is also a typical example of the good results obtained with carbamide in traumatic injury, involving in addition the presence of gross infection.

Case 5.—J. J. L., male, age 45, was first seen at the office October 18, 1937, stating that he had crushed his hand with an air jack hammer while straightening a piece of steel. Examination revealed a three inch laceration on the palmar surface of the right index finger extending from the tip of the distal phalanx to the second palmar crease. The wound was jagged and the adjoining tissues were badly crushed. In addition to the soft tissue injury, there was fragmentation of the bones of the index and second fingers as well as a dislocation of the second phalanx of the first finger. The flexor tendons were exposed throughout the length of the laceration. The wound was débrided under regional anesthesia, the edges sutured as well as possible, and the hand placed on a molded plaster splint. By the third postoperative day, a gross infection developed in the flexor tendon sheath; the wound was opened and packed with carbamide crystals. This was done daily for four days, at the end of which time the wound was clean and granulating. In 10 days' time the wound was completely healed, although traction was maintained on the finger for three weeks, and this was followed by appropriate physiotherapy. Considering the serious tendon sheath infection, the result was excellent, for the only residual disability was a slight limitation of the motion of the second phalanx.

We are still of the opinion that, although the mild bactericidal action of carbamide is of some consequence, the chief value of the compound in wound healing is due to its remarkable solvent action on protein compounds. As Mertins⁹ concludes from his experience with carbamide in chronic otitis media,

"the results are simply due to a more adequate removal of the gross and microscopic debris in the recesses of the middle ear, giving nature a fair chance, often with surprisingly successful results." Dilute urea solutions also continue to be used^{10, 11} with the idea that they stimulate cell proliferation in wound healing.¹² That they give a slight degree of success we cannot deny, and as we have already pointed out this is probably due to the long known activity of dilute urea solutions in promoting proteolysis of the necrotic tissue.¹³ Support is given to this view by a recent study¹⁴ demonstrating that dilute urea solutions are without influence upon the rate of growth of fibroblasts in tissue culture. It is true that there is some evidence¹⁵ that dilute urea solutions produce proliferation of capillaries by sprouting and may thus aid in wound healing. However, we prefer to avoid dilute urea solutions because of the excellent medium for bacterial growth which they provide and the superior results obtained with higher concentrations.

SUMMARY

The efficacy of carbamide (urea) as an adjunct to wound healing, due primarily to the lytic action of strong aqueous solutions upon necrotic tissue and other debris, is again demonstrated. Details of the practical application of carbamide therapy are outlined.

REFERENCES

- ¹ Reid, Mont R.: *ANNALS OF SURGERY*, **105**, 982, 1937.
- ² Christopher, Frederick: *Internat. Clin.*, Vol. 1, n. s., **81**, March, 1938.
- ³ Fantus, Bernard: *The 1937 Year Book of General Therapeutics*, The Year Book Publishers, Inc., Chicago, p. 261.
- ⁴ Holder, Hall G., and MacKay, Eaton, M.: *J.A.M.A.*, **108**, 1167, 1937.
- ⁵ Symmers, W. St.C., and Kirk, T. S.: *Lancet*, **2**, 1237, 1915.
- ⁶ Mertins, Paul S., Jr.: *Arch. Otolaryngol.*, **26**, 509, 1937.
- ⁷ Morgenroth, J., and Ginsberg, S.: *Berl. klin. Wchnschr.*, **1**, 343, 1913.
- ⁸ Dixon, W. E., and De P.: *Jour. Pharm. and Exper. Therap.*, **31**, 407, 1937.
- ⁹ Kilbourne, Normal J.: *Jour. Surg., Gynec., and Obstet.*, **62**, 590, 1936.
- ¹⁰ Lewy, Robert B.: *Arch. Otolaryngol.*, **25**, 178, 1937.
- ¹¹ Bogart, Leon M. J.: *Mich. Med. Soc.*, **36**, 285, 1937.
- ¹² Robinson, William: *Am. Jour. Surg.*, **33**, 192, 1936.
- ¹³ Ramsden, W. J.: *Physiol.*, **28**, 23, 1902.
- ¹⁴ Hetherington, Duncan C., and Shipp, Mary E.: *Proc. Soc. Exper. Biol. and Med.*, **37**, 238, 1937.
- ¹⁵ Abel, Richard: *Anat. Rec., Supplement No. 3*, **67**, 1, 1937.