Medical and Surgical Applications of Collagen

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I. Introduction

THE ENORMOUS RATE at which our knowledge of the structure, chemistry, biochemistry, and biology of collagen has accumulated during the

shaped fabric with the collagen solution. The collagen solution has good biochemical, immunological and clotting properties with minimal platelet adhesion. The long-term survival (more than 8 months) proved the mechanical and biological efficiency of this type of artificial valve.

Summary. Compound collagan–Dacron vessel prostheses with highly porous fabric walls have not only a place in the history of vessel substitutes, but represent a very promising trend in the construction of small-diameter vessel prostheses.

B. Plastic Surgery

The major topic that will be reviewed is the development of "synthetic skin" or more efficient wound dressing materials consisting mainly of collagen. Temporary biological dressings are essential and lifesaving for large skin defects, such as extensive third-degree burns, until permanent repair with autografts or isografts can be instituted (Song *et al.*, 1966). Homografts as well as heterografts have been found to be very valuable methods of therapy. Free skin grafting (Rogers, 1959) with bovine embryo skin (Silvetti *et al.*, 1957; Rogers *et al.*, 1957), canine skin (Switzer, 1966), and pig skin dressing has provided satisfactory results. Another biostructure rich in collagen and successfully used as temporary burn dressing is amniotic membrane (Pigeon, 1960). However, the availability, storage, and sterilization of such products present serious problems.

The development of biologic dressings is strictly empirical. Collagen-rich allografts exert their beneficial effects by (1) controlling evaporation of fluid, thus keeping the wound pliable and flexible; (2) improving heat regulation; (3) promoting the development of viable but not extensive amounts of granulation tissue; (4) mechanical protection against physical and bacterial insults; (5) diminishing pain. As all the allografts mentioned above comply with these criteria, the criteria for optimally functioning biologic dressings must be expanded. Thus, nonantigenicity and nontoxicity are essential, with ease of sterilization, good handling and storing properties, and low expense desirable.

Viability of the skin allograft is not essential to its function (Pruitt and Silverstein, 1971); lyophilized or formalin-treated pig skin is acceptable (Parrish *et al.*, 1964; P. Silverstein, personal communication, 1972). The use of pig skin as a wound dressing material presents several problems, however. Sterilization is difficult: simply treating the cutaneous allografts with antibiotics upon collection at a slaughterhouse would certainly be criticized. As the antigenicity of "collagen" is related more to contamination by noncollagenous components, pig skin, or similar biological dressing materials are potential sources of immunological reactions, especially after repeated use. Besides the immunological problems, the role of skin enzymes, fatty acids and other components in tissue and organ reactivity should be taken into consideration (Rubin and Bongiovi, 1971). For these and other reasons the completely synthetic skin substitutes seem to be the best solution, although not all these materials are satisfactory. As pointed out by Pruitt and Silverstein (1971), "monolayer film and spray plastics such as aeroplast, cellophane, silicone and thermoplastic vinyl polymers studies were unsuccessful due to poor adherence to the wound. Synthetic membranes do not allow firm adherence to the wound, this is the unique property of sponge-like material. Into this category belongs formalinized polyvinyl alcohol (Ivalon) (Hodge and Schmitt, 1960; Watson *et al.*, 1954; Kraissl *et al.*, 1938), velours of nylon, Dacron, rayon (Pickrell, 1939) and Teflon (Ott, 1963)." Their clinical evaluation, however, was complicated by bacterial invasion.

Collagen was tested as a dressing material in the form of bovine collagen gels (Bornstein and Piez, 1966), reconstituted collagen as a brittle sheet 2–3 mm thick (Abbenhaus and Hemenway, 1967), foil laminated to a thin layer of tanned collagen film (Kang *et al.*, 1967), or reconstituted into Dacron mesh (Song *et al.*, 1966). Although Peacock (1961) showed that neutral solutions of collagen, acid collagen gels, and reconstituted collagen did not increase tensile strength in healing incision skin wounds in rats, the use of collagenous materials has several beneficial effects. Large areas of excised skin or third-degree burns were dressed by reconstituted collagen film made from cowhides (Abbenhaus and Donald, 1971); this material was either glued to the skin with methylcyanoacrylate or sutured in place. The perforated collagen film appeared to afford excellent protective coverage for 3–4 weeks, diminished fluid loss and helped maintain sterility. In the burn series, the collagen was equal to autogenous skin grafts in diminishing fluid loss, maintaining sterility and promoting healing. Stoop (1970) treated pressure sores in paraplegic patients with collagen foil (sponge, developed by Braun, Melsungen). He summarized his experiences as follows: (1) After application of the collagen foil the wounds were clean and bacterial infection was retarded. (2) The drainage of wound secretion was diminished. (3) The formation of new granulation tissue was improved (4) The undermined edges of the pressure sores were closed. (5) The formation of the epithelium was stimulated. (6) The closed wounds showed no contractures. (7) Moist pressure sore fissures which showed no tendency to heal were closed. (8) Immunological reactions toward the collagen were not observed. (9) The general condition of the patient was improved.

Knoll and Friederich (1969) employed a thin collagen film (Braun) as temporary wound dressing for skin defects. The films were fixed

tissue, they may be the source of epileptic seizures, neuralgic pains, and intestinal obstruction. The biologic background for adhesion formation is activation of fibrogenic cells to produce collagenous structures which glue two surfaces together.

Several materials have been used to prevent adhesion formation; among them are membranes such as fascia lata, and films of gelatin, agar, and fibrin. Millipore membranes made of acetylcellulose have been widely used even though they are nonresorbable and must be surgically removed.

Films made of collagen or gelatin are absorbable and show minimal tissue reaction. Braun (1964) reports on the successful use of collagen film in neurorhaphy of transected sciatic nerve in the rat. Samohyl *et al.* (1970) used collagen membranes to prevent adhesions following injury to the common digital flexor tendon in the guinea pig forefoot. The membrane was impregnated with heparin to decrease the local inflammatory response associated with wound healing. This appears to delay by 4–5 days the time of most rapid collagen synthesis in healing wounds (Thompson *et al.*, 1972). Wrapping the tendon with a heparinized collagen membrane prevented healing of the tendon stumps; inserting the membrane underneath the tendon prevented concretion with surrounding tissues as well as fusion of the stump by newly formed connective tissue.

M. Gelatin–Resorcinol–Glutaraldehyde Tissue Adhesive

Although this application does not deal strictly with collagen, we are including it in our review as gelatin is certainly derived from collagen. This material represents a very interesting field from both theoretical and practical points of view.

As mentioned by Cooper and Falb (1968) there are at least four reasons why surgeons try to replace a suture by adhesive bonds: the procedure is rapid, provides complete sealing and prevents seepage of fluids, permits bond formation without undue deformation of tissue, and has the potential to augment physically weakened tissues (aneurysms). A sound tissue adhesive should be nontoxic, form a strong, adherent bond, and stay elastic after polymerization. It should be biodegradable so that after serving its supportive function it is absorbed and does not form a barrier to healing.

Gelatin was tested because of its chemical resemblance to connective tissue and its adhesive properties. Tanning the gelatin glue with formaldehyde on the tissue surface was unsatisfactory because bond strength fell off rapidly. Addition of resorcinol provided the advantage of increasing the fluidity of the gelatin solutions (Cooper and Falb, 1968). These authors found a suitable ratio of gelatin to resorcinol to be 3:1, with 18% formaldehyde present and with the content of solids amounting to 60–70%. This compound was found useful both as a tissue adhesive and hemostatic agent with minimal adverse reactions (Braunwald and Tatooles, 1965; Braunwald *et al.*, 1966). Resorcinol, like most phenol related plastic materials, polymerized into a meshwork in the presence of formaldehyde with the release of water molecules. Gelatin has the function of a filling matrix which is responsible for the rubberlike elasticity of the adhesive (Lemperle *et al.*, 1967). Experimentally, it was found that cross-linked gelatin as a tissue adhesive and hemostatic agent binds rapidly to the living tissue without being irritating or necrogenic. The bond is not altered by the presence of moisture and is almost insoluble in body fluids. Later Tatooles and Braunwald (1966) suggested raising the local pH to 7.0 by bicarbonate, which initiates an immediate cross-linking.

Finally, it was suggested that formaldehyde might be replaced with less toxic glutaraldehyde to minimize the effects of the cross-linking agent on the tissue (for review, see Morgenstern, 1967).

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References

Abbenhaus, J. A., and Donald, P. (1971). *Laryngoscope* 81, 1650.
Abbenhaus, J. A., and Hemenway, W. G. (1967). *Surg. Forum* 18, 490.
Adam, M., and Kühn, K. (1968). *Eur. J. Biochem.* 3, 407.
Adam, M., Deyl, Z., and Rosmus, J. (1970). "Interaction of Metals with Collagen," Vol. 80, p. 1. Czechoslovak Acad. Sci. Publ. Co.
Adler, R. H., Pelecanos, N. T., Geil, R. G., Rosenzweig, S. E., and Thorsell, H. G. (1962). *Surg. Forum* 13, 29.
Alvares, J., Parsonnet, V., and Khatami, M. (1966). *J. Newark Beth Isr. Hosp.* 17, 3.
Apt, L., Costenbader, F. D., and Parks, M. M. (1960). *Arch. Ophthalmol.* 63, 30.
Apt, L., Costenbader, F. D., and Parks, M. M. (1961). *Arch. Ophthalmol.* 65, 474.
Apunay, M. B., and Tanner, J. C. (1969). *Surg. Forum* 20, 483.
Arnon, R., and Sela, M. (1960). *Biochem. J.* 75, 103.
Artandi, C. (1964a). *Bull. Parenteral Drug. Ass.* 18, (No. 5) 2.
Artandi, C. (1964b). U.S. Patent 3,157,524.
Artandi, C. (1967). *Isotop. Radiat. Technol.* 4, 399.
Assefi, I., and Parsonnet, V. (1964). *J. Newark Beth Isr. Hosp.* 15, 161.
Bailey, A. J. (1967). *Radiat. Res.* 31, 206.
Bailey, A. J. (1968). *Int. Rev. Connect. Tissue Res.* 4, 268.
Bailey, A. J., and Peach, C. M. (1968). *Biochem. Biophys. Res. Commun.* 33, 812.
Bailey, A. J., Bendall, J. R., and Rhodes, D. N. (1962). *Int. J. Appl. Radiat. Isotop.* 13, 131.
Bailey, A. J., Fowler, L. J., and Peach, C. M. (1969). *Biochem. Biophys. Res. Commun.* 35, 663.
Balazs, E. A., and Sweeney, D. B. (1968). *In* "New and Controversial Aspects of Retinal Detachment" (A. McPherson, ed.), p. 371. Harper, New York.