

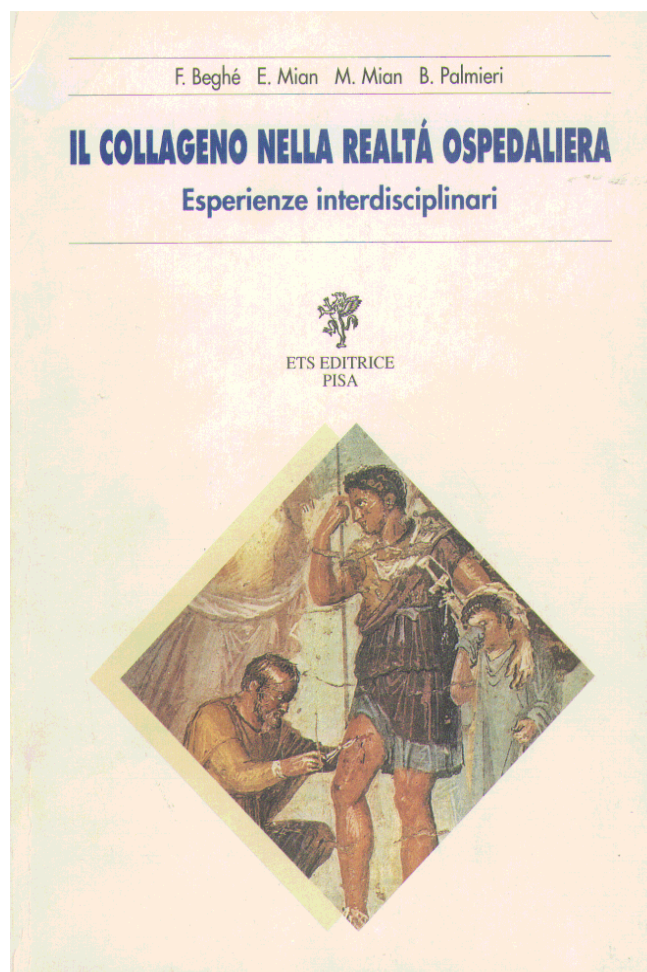
Abstracts from the book:

IL COLLAGENO NELLA REALTA' OSPEDALIERA

Esperienze interdisciplinari

F.Beghè, E.Mian, M. Mian, B.Palmieri

"Collagen in hospital practice"
Abstracts from several domestic and international Congresses



FOREWORD

In the listed clinical experiences and trials, the Euroresearch's collagen sponge is mentioned – other than as BIOPAD® – using different brand names and trademarks merely for marketing purposes, amongst which Condress®, Gelfix®, Proteita®, and sometimes with the laboratory codes BG PRG, EU 10102.

All these brand names (*property of Euroresearch*), identify the same collagen sponge undergoing the same manufacturing process, in the same facility and with the same identical composition and dosage.

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LOWER LIMBS ULCERS OF VARIOUS ETIOLOGY

Topical conservative treatment with collagen

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Among others the collagen has the property to enhance the tissue repair in wounds. This takes place through different mechanisms such as the stabilization of tissues during the repair phase through a fibrils net able to direct the fibroblasts, the capacity to catch the fibronectin, the glycosaminoglycans and the growth factors or finally to favour the cells migration (1,3,4, 5,6,7,8).

It is therefore justified and rationally correct a therapeutical approach suggesting the use of heterologous lyophilized collagen in the treatment of lower limbs ulcers with vascular pathogenesis. Moreover the clinical evaluation of the effects of collagen in the repair process of these lesions can be criticized due to the low homogeneity of the examined cases (ulcers with similar etiopathogenesis in different patients, ulcers in areas of the same patient where macro and microcirculation conditions may remarkably vary).

In the past years we fixed an experimental clinical study protocol which enabled to evaluate the therapeutical efficacy of the heterologous lyophilized collagen comparing it to a compound (hydrocolloid) commonly used in the treatment of lower limbs ulcers (2).

This protocol, which implied the use of both compounds on the same lesion or on the same patient in case of multiple lesions, enabled us to prove how the recovery speed of the lesion (mm/week) was significantly higher for the collagen compared to that of the control medicament independently from the etiology of the lesions ($p < 0.001$), even considering only the venous etiology cases ($p < 0.05$).

Based on these results we have treated 96 patients (from January 1 1990 to March 1 1992), affected by lower limbs ulcers of different etiology (Tab. 1-2). Common blood analyses and Doppler arteriography were included: in 78 cases the etiology of the ulcer was due to venous insufficiency to lower limbs; in the remaining 18 cases it depended on arteriopathy or mixed causes that is a venous insufficiency bound to an arterial one (6 patients). Once performed the topical cleansing, the ulcers were treated with lyophilized collagen.

In association with the local treatment of the lesions, patients with ulcers caused by venous chronic stasis were subject to an elasto-compressive bandage, whereas in cases with arteriosclerotic or mixed etiology metabolic controls and eventually a surgical revascularization were performed (Tab. 3).

All patients were followed in the time and controlled weekly during 3 months from recruitment.

Results are expressed in percentage and evaluated at the 28th, 66th and 90th day (Tab. 4).

The analysis of collected data shows that the best results were obtained in patients affected by venous stasis pathologies: in fact after 4 weeks of treatment 65.3% of the lesions was healed whereas at the control at 90 days the recovery percentage rose progressively to 100% (85.8% at 56 days).

83.3% of the lesions due to pure ischemic etio-pathogenesis were healed at 90 days, whereas 66.13% of mixed ulcers reached healing.

The only two patients that at the follow up resulted not healed from ischemic ulcers were respectively a femoral popliteal by-pass case (Tab. 3) and the only patient within the group who did not undergo surgery (Tab. 2). Both patients showed a significant reduction of the size of the lesion and of the symptoms.

The treatment of lesions with mixed etiology appeared to be more difficult and gave poorer results. As a demonstration of the importance of the correction of etiopathogenetic factors causing difficulties in the treatment of ulcers we have the case of a female patient practically unchanged at the 56th day, and reevaluated after an arteriography. It was performed a TEA open sky of the deep femoral artery homolateral to the perimalleolar lesion. The surgical operation was initially not favourably considered in view of the extension and calcification of the arterial lesions. The revascularization enabled the healing of the perimalleolar ulcer treated with the heterologous lyophilized collagen during two weeks.

In our experience the gradual reduction of the size of the lesion is always associated with a significant and fast reduction of subject symptomatology. The products of collagen disaggregation never favoured clinically detectable bacterial proliferations.

The heterologous lyophilized collagen therefore demonstrated to favour, in our patients, the healing of trophic lesions from venous stasis of the lower limbs, sensibly increasing the reepithelialization speed; such property was also evident in patients suffering from secondary lesions from arteriosclerotic pathology or mixed etiology provided the drug could act on tissues with good blood supply and oxygenation.

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Table 1

Males	31 (32%)	Mean age 64.5 years
Females	65 (68%)	Mean age 66.7 years

Table 2

TYPE OF LESION	NR OF CASES	ASSOCIATED INTERVENTIONS	NOT SUBJECTED TO INTERVENTION
Venous etiology	78	1	77
Arterial etiology	12	11	1
Mixed etiology	6	1	5
Total	96	13	83

Table 3 - Associated surgical interventions

Popliteal vein trapping	1
Aortho-bifemoral by-pass	4
Femoral-popliteal by-pass	4
Femoral-tibial by-pass	1
TEA* deep or superficial femoral artery	2

*TEA = thrombo endo arteriectomy

Table 4

Follow up	Total	Venous etiology	Arterial etiology	Mixed etiology
28 days	58.0% (56/96)	65.3% (51/78)	33.0% (4/12)	16.6% (1/6)
56 days	79.0% (76/96)	85.8% (67/78)	58.0% (7/12)	33.0% (2/6)
90 days	95.8% (92/96)	100% (78/78)	83.3% (10/12)	66.6% (4/6)



Fig. 1
Pre-tibial venous ulcer prior to treatment



Fig. 2
A collagen sponge is positioned in direct contact to the lesion, to completely fill the ulcer cavity (control at 14 days)

Fig. 3
Recovery of the lesion
(final control after 56 days)



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HETEROLOGOUS COLLAGEN IN ORTHOPEDICS AND TRAUMATOLOGY

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Since a number of years the heterologous collagen is used in various orthopedic and traumatological situations. The pathologies we face are rather wide and sometimes are borderline with other medical fields. For this reason we have used the collagen also in metabolic, vascular and neuropathic pathologies (diabetic foot, trophic ulcers, pressure ulcers).

The orthopedic or traumatized patient may be diabetic or vasculopathic; he may bear peripheral neuropathies or pathologies confining him in bed: all situations where the lesion, the decubitus and the ulcer are frequently present.

The indications where we have used the collagen are the following:

1. traumatic lesions, superficial or deep; traumatic amputations of limbs etc..;
2. cutaneous lesions from metabolic diseases, such as diabetic foot;
3. vascular lesions, such as trophic ulcers and some diabetic lesions due to microangiitis;
4. neuropathic lesions, such as some sores and ulcers to the foot of alcoholic;
5. microtraumatic lesions, where the mechanic element is variously involved together with other conditions such as sacral decubitus or calcaneum decubitus in bed-ridden patients;
6. another recent satisfactory application involves hemostasis in the surgery of hand (Dupuytren disease etc..) after detachment of the pneumatic lace.

In many situations the ulcer, the sore and the decubitus are the final result of mechanic, vascular, nervous and metabolic factors, alternatively prevailing.

Which is the role of primary metabolic alterations in diabetic foot? Which is the role of microangiitis? of neuropathy? of the mechanic element?

If it is true that the therapy must be etiologic it is also true that the cutaneous lesion, clinical epiphenomenon, may find a common denominator in treatment: this is the collagen.

Using collagen in orthopedics and traumatology a rigid protocol was not applicable: too different the lesions per size, site and depth, too different the variations of a situation compared to another one.

We have followed these general rules:

- cleansing, before application, with physiologic solution only; eventual curettage of the bottom and of necrotic edges; never use disinfectants;
- medications with sponges of collagen to cover the lesion holding it with plasters on integral skin;
- change of medication initially every 24-48 hours, then 2-3 times per week;
- application possibly on cleansed lesions, but also on contaminated bottom.

From the experience made in these last years on over 60 cases we came to these conclusions:

- collagen promotes and accelerates the tissue repair process;
- it can rapidly fill the gap between the bed of the lesion and the epidermal plane;
- it frequently brings to complete healing without the help of other treatments;
- it creates an ideal bed to the attachment of dermo-epidermic skin-grafts;
- on a suspect or contaminated ground, it often shows a good cleansing capacity ("biological curettage")

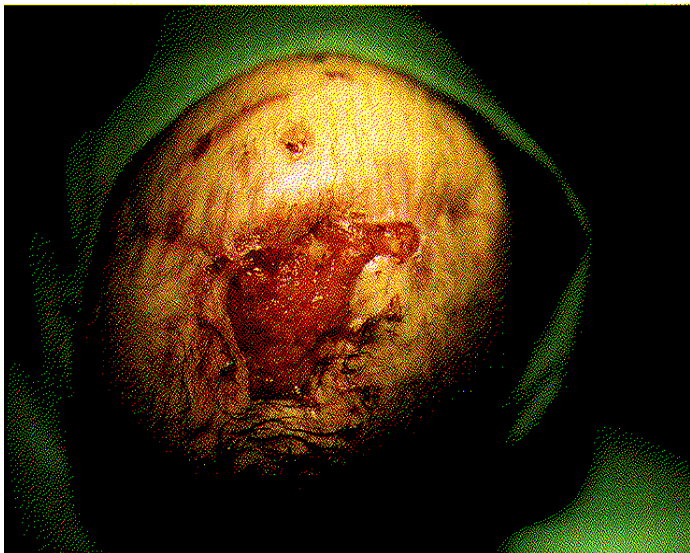
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A)
M.P. 18 years old - Amputation of the thigh following a motorcycle accident; the bone stump could not be shortened in view of a subsequent prosthesis. Hoping in a second intention recovery we performed a traction on the skin with protected stitches and laid the collagen sponges.



B)
After 4 weeks of treatment the necrotic areas were cleansed; it is still visible the section plane of the femoral diaphysis.



C)
After 45 days the uncovered area is very reduced and well cleansed. Complete healing was reached after other 15 days.



D)
Complete recovery, after 60 days

THE ROLE OF HETEROLOGOUS COLLAGEN

In the healing of residual post-operative cavities

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The recent acquisitions on the cytologic and biochemical aspects of the regeneration and tissue repair processes led to valorise the role of collagen in healing processes (David and Berfield, Tooke, Clark). The exogenous support of a collagenic scaffolding anchors and directs the fibroblasts, reduces the degradation of the glycosaminoglycans of the basal epithelial membrane, modulates the production of collagenesis and finally traps in the regeneration area fibronectine, glycosaminoglycans and growth factors. The remarkable biocompatibility of collagen and the role it plays in the tissue repair process suggested its pharmacological use in order to accelerate the physiologic healing processes. In general surgery many situations take advantage of the use of heterologous collagen, among which the residual post-excisional cavity of pylonidal sinus and the perianal cavity after rectotomy. They constitute clinical models suitable to verify in clinical practice the efficacy of subject drug in favoring the tissular regeneration processes and finally the faster repair of the remarkable post-operative losses of substance.

From 1986 to 1991, at the First Chair of Surgical Anatomy and Surgery Courses of the University of Catania we observed 96 cases of pylonidal fistulas. Twenty-one patients healed for primary closure and 75 for secondary intention. Twenty-six patients were treated with pads of lyophilized heterologous collagen.

After the sinus excision and the closure of the residual sacro-coccigeal cavity to reach haemostasis, same was re-opened on fourth day. After 12-24 days and complete cleansing of the cavity and formation of granulation tissue, some collagen pads were laid on the granulating bed of the lesion to form a uniform layer and then covered with a compressive bandage. These medications were repeated on alternate days until complete healing.

After 48 hours from previous medication the collagen sponge was no more macroscopically recognizable being embedded in the fibrino-haemorrhagic layer, fully undistinguishable from the surrounding granulation tissue except the peripheral parts due to a pale pink colour compared to nearby tissues.

This implied a reduction of the residual cavity at an extent al most corresponding to the thickness of the pad used. The scarification of the surface covered by the collagen provoked a "cup" type haemorrhage, showing its incorporation in a very vascularized granulation tissue. The subsequent medications on alternate days showed even better the evolution of this phenomenon.

According to the entity and rapidity of these processes, variable from patient to patient, the pads were applied one every 3-5 days.

The histological control of the granulation tissue, performed in 9 patients 48 hours after the last application of collagen, evidenced the complete dissolution of the collagen pad itself and an intense granulation with lympho-plasma-cell and granulocytic infiltrates.

In conclusion the excision of pilonidal fistulas, with healing by secondary closure, although offering higher success possibilities (relapse rate 0-12% - Akawari, Al-Hassan and Coll., Azab and Coll.) sometimes protracts, even remarkably, the healing time. Our 21 patients who healed by primary closure showed a healing time of 12 ± 3.99 days, with a 23% relapse rate. The 49 patients who healed by secondary closure showed longer healing time, between 2-4 months, with a 0% relapse rate.

In the 26 cases who healed by secondary closure with application of collagen, the healing time was remarkably reduced, between 5 weeks and 2 months, with no relapses.

The treatment of the residual cavity after rectotomy although of different clinical aspect, is practically similar on the experimental model.

The clinical peculiarity of the post-abdominoperineal cavity is bound to general factors, to the local invasion of neoplastic disease, to the larger loss of substance and sometimes to the inflammation of the perineal cavity itself.

The ideal rectotomy by abdominoperineal way usually implies the simple primary closure of the residual cavity.

Sometimes (7.1% - Altemeier and Col.) an inaccurate intestinal preparation, a not adequate surgical technique with formation of an hematoma in the upper pelvis-rectum space or in the ischio-rectal cavity, the scarce attention to absolute asepticity until the perineal time of the intervention easily lead to suppurative complications which required drainage. In order to avoid this eventuality, whenever healing for primary closure is doubtful, it is possible to perform treatment by secondary intention. In any case the repair of the residual cavity needs a very long time.

From 1986 to 1991 we performed rectum resection for carcinoma on 39 patients aged between 43 and 77 years. The healing of the residual cavity occurred on 19 patients by primary closure; in 11 cases the cavity had to be reopened whilst in 9 cases healing was reached by secondary closure.

The patients who underwent the reopening of the cavity by cause of a suppurative process (11 cases) were treated daily with repeated washes of the residual cavity during 15-20 days. Only after complete cleansing of the cavity and growth of granulation tissue, we treated 4 patients with applications of collagen pads kept with a compressive bandage. These medications were repeated every other day until complete healing. According to the entity and speed of these processes the pads were applied one every 3-7 days. Three of the 9 patients who healed by secondary closure were treated with collagen pads, as an average 10-14 days after surgery.

The patients who underwent the reopening of the residual cavity and were medicated without collagen (7 cases) healed in a range of time between 3 and 5 months; those treated with collagen (4 cases) healed after 2-3 months.

Among the patients who healed by secondary closure, medicated without collagen (6 cases), the healing time was ranging between 2-4 months, whilst those treated with collagen healed after 1,5-2 months.

Therefore the suppuration of the residual cavity - requiring the complete cleansing of the abscess - significantly protracted the healing time. The complete control of sepsis allowed a fast repair of the loss of substance, favoured by the application of collagen pads. On the other hand, in the patients who healed by secondary closure the absence of suppurative processes favoured a faster granulation, accelerated by the use of collagen (Fig. 1-2 and 3).



Fig. 1

Fig. 1 - Healing by second intention of the residual perineal cavity after rectotomy. Aspect of the cavity, already granulating on the 20th post-operative day



Fig. 2

Fig. 2 - Residual cavity after rectotomy. 30th post-operative day. The collagen pad, 24 hours after its application is already incorporated in the tissue, where is still recognizable.



Fig. 3

Fig. 3 - Same case shown in fig. 2. After 48 hours, the collagen is no more recognizable unless for the pale pink color on the bottom of the cavity where it was applied.

It must be noted however that the regeneration and repair processes are strongly influenced not only by local factors connected to the cleansing of the residual cavity, but also by general parameters such as age, anaemia and malnutrition, whose correction is essential to the success of the local treatment.

Finally, the healing of large post-operative losses of substance is favoured by the application of heterologous collagen, with a remarkable reduction of the repair time. The cleansing of the cavity and the application of the collagen on a well granulating tissue are essential local conditions to the success of the treatment.

This requires a free interval between surgery and beginning of treatment, variable from person to person, depending on the evolution of the residual cavity, on the speed and intensity of the granulation process and on the eventual presence of previous or superimposed infections.

This hinders the formulation of precise terms on the beginning of the treatment, whose evaluation is mainly clinical. However once the application of collagen is started, both in case of pilonidal sinus and post-rectotomy cavity, a significant reduction of healing time is recorded, thus demonstrating clinically the efficacy of the use of heterologous collagen in the healing of post-operative cavities.

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THALASSEMIA AND MALLEOLAR ULCERS

Their therapy with heterologous collagen

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It is well known that malleolar ulcers, surely no more frequent as in the past, have always been widely discussed among different surgical and angiological schools. The argument under discussion covered both the etiopathogenetic location and the therapeutic approach.

This pathology is worsened when the malleolar ulcers are associated with hemopathies. Associations between hematologic diseases and malleolar lesions (sometimes severely disabling) are frequently reported in literature.

The difficulties in putting in order this kind of lesions consist mainly in the relative rareness of hemopathic ulcers and in a series of aggravations complicating their evaluation, such as a disease belonging to precise geographic areas, the fortuity of the lesion not always belonging to the main symptomatology, the therapy of the wound mainly concentrated on the hematologic aspect than directly on the ulcer and finally the positioning of the ulcer itself as a dermatological lesion, consequently not adequately treated.

We report herebelow our experience on 38 patients affected by thalassemia and malleolar ulcers.

These 38 patients, 24 males and 14 females aged between 14 and 38 years, underwent a careful clinical and physio-pathological investigation.

The ulcer - always occurring on malleolus - was located in different areas, either on the medial or side zone, in one leg or bilaterally. In particular, 6 patients had a bilateral ulcer in the internal malleoli only; 6 patients were affected by an external ulcer to the right leg, 12 had an internal ulcer to the right leg, 6 to the left leg, 5 an external ulcer to the same leg and finally 3 patients had a double ulcer to the same leg. Clinically, the onset of the lesion dated about 3 years back, preceded by chromodermatosis with melanotic characteristics, hardening of derm and thinning of the skin. 50% of patients was splenectomized; the same percentage of patients underwent monthly transfusions whilst 25% received bimonthly transfusions and the remaining 25% was never transfused.

At the time of the first ambulatory visit the patients underwent a series of hemorheologic investigations: erythrocytary filtration, viscometry and a venous and arterial haemo-gas analysis. Even for this second series of patients the results were the same as previously recorded; in fact the haemo-gas analysis was firstly performed taking blood from a peripheral vein and then from the radial artery. Assuming that the O₂ variations near the lesion could be significant, we took blood also from the saphena intubated to malleolus for recording the venous pression. With this procedure it was possible to measure the different O₂ saturation between artery and vein, both at systemic level and directly near to the lesion.

Based on the experience achieved on post-thrombotic syndrome we extended the measurement of venous pressure also to these patients. The first data recorded was a constant hypertension in clinostatism (min. 5 mmHg, max. 24 mmHg, mean 15/20 mmHg).

Another important datum is that in many cases the hypertension was present also in the rear lateral limb, in clinostatism, even in the absence of ulcerous lesions. On the contrary, in orthostatism the minimum pressure recorded was 2 mmHg, and the maximum was 6 mmHg, with an average of 3.8 mmHg. Another peculiarity evidenced by the orthodynamic test was the total absence of pressure decrease in 8 patients, whilst in the others we noticed a decrease of the pressure values with a curve showing a good emptying of the superficial circulus.

A peculiarity of all the diagrams was the presence of a pulsating curve synchronous to the pulse both in ortho and clinostatism. This data initially led us to suspect an arterial-venous fistula, but the arteriography excluded this eventuality evidencing at the same time the permeability of the refluent venous circulus in the absence of anomalies justifying both hypertension and pulsing rythm. It is not easy, based on the results so far achieved, to explain correctly and completely the genesis of the malleolar ulcers of these patients; surely hypoxia has a prevailing role acting on the decrease of normal hemoglobin associated to a bad peripheral oxygenation and on anomalous rheologic behaviour of the thalassemic erythrocytes, as shown by filtration results.

In fact the increase of these values would derive both from the different shape and volume of red corpuscles and from the increase of stiffness of their cell membrane. To this it must be added that the foetal hemoglobin present in the erythrocytes of thalassemic subjects has a strong affinity to the O_2 that is then released to tissues in a more difficult way. Surely the newest and more important datum is the venous hypertone recorded manometrically, along with the pulsing wave whose genesis is of difficult interpretation. It can be hypothesized - even if not experimentally validated - that cardiac insufficiency bound to sclerotic degenerative phenomena to myocardium, often present in these patients, plays a prevailing role in causing the recorded phenomena.

In the light of what precedes, our therapy aimed both to control the venous hypertone using an elastic constriction (alike in the treatment of the post-phlebitic syndrome) and to improve the microcirculation acting on the changeability and plasticity of the red corpuscle with Pentoxifylline.

To these therapies we added the use of heterologous collagen. The product is so easy to apply on the ulcers that the patient himself can continue the treatment at home; the complete absence of side effects and above all the short healing time led us to extend the use of this device to all our patients under observation. All lesions were ulcers, with variable size from 1x1 cm to 6x4 cm. Due to the characteristic etiopathogenetic complexity of the ulcer it is not possible to compare the different healing times between lesions of similar sizes treated or not with collagen: we could however observe that the ulcers treated with collagen heal in a shorter time and, what is most important, that the ulcer once healed is no more recurring while in patients not treated with collagen the relapse was extremely recurrent.

In fig. 1-2-3 is shown the typical evolution of a malleolar ulcer in thalassemic subject, from onset to complete healing.



Typical evolution of a malleolar ulcer
In thalassemic patient



Surely there are still many obscure aspects in the pathogenesis of malleolar ulcer in thalassemic patients and the results so far achieved are sometime conflicting and of difficult interpretation.

It is anyway sure that the use of collagen has significantly helped in speeding up the healing of this type of lesions with simple techniques and great satisfaction of both patient and doctor.

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HETEROLOGOUS COLLAGEN AND KERATINOCYTES IN THE TREATMENT OF DIABETIC ULCERS

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Used in over than 100 cases of diabetic gangrene, 65% of which from 3rd to 5th degree of Boulton scale - that is deep infection up to bone level, extended to a wide area of the foot - the collagen confirmed the excellent positive results given since the beginning in the repair process of lesioned tissues and cicatrization of ulcers previously cleansed by debridement.

The collagen sponge is very easy to use both on surface and deeply in excisions, fistulas, drainage, pouches, in all the course and in early treatment as haemostat, suitable to keep vital bone stumps or exposed tendons, during cleansing to stimulate granulation and new angiogenesis up to cicatrization phase.

The experience achieved proved the activation of local defenses against the infection always present in diabetic ulcers often until the cicatrization phase, as proved by the microbiological test for long positive. With the collagen we can reach healing in spite of the presence of antibiotic resistant germs during the whole treatment period. Healing moves from the most cleansed areas, generally the edges of the lesion, progressively reducing the size of the infected area until complete recovery.

Dissolved and absorbed in situ, the collagen lays down on the wound a semi-permeable membrane to protect and stimulate the regeneration tissues, maintaining the ideal microenvironment conditions where the growth factors can develop their activity, preventing superinfections and cellular degeneration during the long time required by the slow reepithelialization process. The collagen must never be removed and it is applied with decreasing frequency following its lysis, determined by the quantity and type of exudate of the ulcer. The medication technique is easier, the more so in home-made treatment, and pain for the patient is sensibly reduced.

The cost-benefit ratio is extremely favourable as regards the higher possibilities of ambulatory treatment of diabetic gangrene due to the easiness of use of collagen, the reduced number of medications which can also be performed by the patient himself, the safety and protection guarantees offered by the product. The use of collagen allows to reduce the hospitalization time whenever it is unavoidable.

Once consolidated my experience in the use of heterologous lyophilized collagen, I tested thin layers of human keratinocytes, grafted on gauze, frozen at -80°C , brought to 37°C in thermoregulated bath at the time of medication. The idea was to obtain an additional stimulus to the consolidation of the granulation tissue to the bottom of the lesion, therefore a synergism of action with the collagen in the tissue repair and a spur to reepithelialization moving from the edges of the ulcer. The efficacy of the treatment is limited to the first applications kept in situ during 5 days and to a careful cleansing of the wound, obtained with the use of collagen.

Another experience on the synergism between collagen and keratinocytes is given by the simultaneous use of the two medicaments on deep wounds or in presence of exposed fascias or tendons, where the keratinocytes cannot adhere. In these cases the collagen sponge provides the optimal filling support or anchoring to the epithelial edge which can perform its action.

Aware of these technologies, we can propose the collagen, for its multiple characteristics, as a product of high therapeutic value and wide use, eventually associated with other medicaments able to enhance its activity.

As an example of the experiences made, the case of a wide plantar lesion deeply excised, after amputation of the second toe due to a focus of infection with fast centripetal propagation, which required the extirpation of a large part of the fascia (Fig. 1). The use of collagen in the excision wound allowed the fast closure and the filling with granulation tissue (Fig. 2); the application of layers of keratinocytes has consolidated that result and stimulated the reepithelialization from the edges of the ulcer (Fig. 3).



Fig. 1



Fig. 2



Fig. 3

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HETEROLOGOUS COLLAGEN

Pharmacological update

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In the last years a series of studies on the biology of cicatrization enabled to reach more accurate and specific knowledges.

Which are their basis? We summarize the following:

- * cicatrization starts "immediately" after the lesion occurs, almost at the same time when clotting and haemostasis take place;
- * there are many biological systems playing a role in cicatrization: clotting, haemostasis, inflammation, immunity, complement system etc..;
- * many cell types play an important role in the sequence of the repair phenomena: platelets, neutrophils, macrophages, mast-cells, fibroblasts and endothelial cells; many of these activities take place thanks to the so-called growth factors (PDGF, TGF α and β , TNF α , FGF, IGF 1 and 2, EGF) having a mitogenic and chemotactic activity;
- * the mitogenic and chemotactic activities of the growth factors enhance the proliferation and the migration of epithelial cells of fibroblasts and of endothelial cells;
- * there is a precise sequence of the events in the healing process but apart the well known phenomena starting the repairing process, those responsible of its final phase are still unknown;
- * other substances may control the different phases of tissue repair like the lymphokynes and the extra-cellular matrix itself in its collagenic and not collagenic component (fibronectin).

These knowledges determined the definition of an actual "pharmacology of wound healing", thus meaning the study of the mechanisms of action of biological, chemical and physical agents able to accelerate or decelerate the tissue repair process.

In parallel the concepts of "scarring modulation" or "driven scarring" have developed, meaning the possibility to interfere in the repair phenomena in order to optimize healing.

The collagen, initially used as simple filler, has now taken the physiological role of modulator of the tissue repair process: we are no longer speaking about a passive role as a simple product of the fibroblast biosynthetic activity, but an active role as regulating factor exerted by said protein and interactive in respect to cytokines, fibronectin and growth factors.

From all the above we can understand the opportunity to use the heterologous lyophilized collagen in order to accelerate the tissue repair process, or stimulate it when delayed.

Many experimental studies prove the activity of the heterologous lyophilized collagen as healing dressing. Already in the 80's M. Chvapil outlined the capacity of collagens to enhance the tissue repair and the reepithelialization of wounded areas either in the rat and in guinea pig, activating the inflammatory phase of the healing process and the new vessels formation.

Subsequent studies by G.Motta and coll. on experimental gastric and cholic lesions in the rat evidenced the ability of collagen in stimulating an orderly fibroblastic proliferation.

More recent studies by M. Mian and coll. on the healing of lesions experimentally induced in the rat prove the activity of heterologous lyophilized collagen and its remarkable superiority over polyurethane sponges. Studies carried out with electron and scanning microscopy support the remarkable chemotactic activity on cells like platelets and monocytes when collagen is implanted in the abdomen or subcutaneously in rat.

Studies performed on pigs subjected to lung transplants where the collagen was used to protect the bronchial anastomosis, showed a larger migration of fibroblasts and active microangiogenesis in the treated anastomotic site compared to the control one.

The results obtained using collagenic substrates in the induction of adhesiveness, differentiation and growth of osteoblastic human cells and particularly of SAOS-2 cells characterized by osteoblastic phenotype but without osteocalcin are of great interest.

These in vitro studies evidenced the stimulating effect of collagenic substrate on the cells adhesiveness and growth, as well as on the differentiation as shown by the newly acquired capacity of the SAOS cells to produce osteocalcin.

In the light of what precedes the following mechanisms of action of collagen are recognized:

- 1) haemostatic effect and interaction with platelets, these last very important in tissue repair as a tank for growth factors; also important the interaction collagen-fibrinogen;
- 2) interaction with the inflammatory response with increase of cells due to chemotaxis of monocyte-macrophages, also important producers of growth factors;
- 3) capacity to act as a mechanical support, a scaffold inducing and orientating the fibroblastic proliferation, and as a modulator of the granulation tissue;
- 4) interaction with fibronectin and other non collagenic proteins;
- 5) enhancer of the adhesiveness, proliferation and differentiation of cultured osteoblastic cells.

Based on the experimental results and on biological conditions, many indications for subject biomaterial can be identified: treatment of chronic vascular ulcers and pressure sores, haemostasis, surgical applications and treatment of burns, these last supported by experimental animal data.

The clinical practice in patients suffering from vascular ulcers (fig. 1) or pressure sores (fig. 2) confirms the efficacy of the heterologous lyophilized collagen which represents a notable mean to solve such severe pathologies.



Fig. 1 - Foot ulcer in a diabetic patient. Complete healing after 3 months treatment with lyophilized heterologous collagen



Fig. 2 - Wide decubitus lesion. The same ulcer after 28 days of treatment with collagen, photo taken at the time the patient was dismissed.

VASCULAR ULCERS

OUR EXPERIENCE USING HETEROLOGOUS COLLAGEN

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It is well known that the organic complications in vascular pathology are consequences of ischemia and stasis: both may bring to the formation of ulcers. Vascular ulcers represent the final act of the microvasal tissue disorder caused by the two above processes.

There are ischemic and phlebostatic ulcers, but quite often they may coexist and in this case the so called mixed ulcers take place. We demonstrated in other studies how the stasis may influence and condition the tissular response to the ischemic insult thus worsening its evolution.

Ischemic ulcers are a typical clinical evidence of an artheriopathy and quite often appear in acral position. The site of the ulcer may change due to the microtraumas in other areas which become the site of origin of the ulcer. Ischemia means a situation where the blood flow is not sufficient to meet the tissues demand. In a tentative of metabolic compensation a massive arterial vasodilation occurs with bad distribution of the flow and presence of not sufficiently fed or not fed capillary vessels in any case malfunctioning. If the bed of the lesion increases, the flow speed slows down and microtrombus appear also caused by leukocytes already activated in their flow on wounded arteriosclerotic areas. To this haemodynamic situation contribute various endothelial, platelets and leukocytary factors, with spastic and antispastic activities; moreover tissular factors occur provoking a direct local damage.

Stasis ulcers are determined by an unbalance between increased microvasal capacity and reduced flush. This is a dynamic phenomenon characterized by the change of the haematic flow rate from high speed laminar to low speed turbulent. It is determined an increase of the permeability with exit of macromolecules including fibrinogen responsible of the formation of pericapillary fibrin couplings which, due to the reduced local fibrinolytic activity, form a barrier to the blood tissue exchanges with hypoxia which is the basis of the ulcer formation.

Also leukocytes may concur to ulcers formation distributing themselves in a chaotic way at the end of the vessels binding to the endothelial receptors and releasing in the perivasal area free radicals of the oxygen which would activate chain enzymatic reactions able to damage vessels and the vasal interspace where other leukocytes form a barrier. In the treatment of ulcers it is of primary importance to correct simultaneously the basal haemodynamic situation and the local infection quite always present.

Only after having modified them and having cleansed the ulcer, the repair can take place.

In our experience the heterologous lyophilized collagen has proven to be remarkably important.

It is a sponge, to be directly put over the surface of the lesion in order to act as a stimulator of the growth of granulation tissue and of epithelial cells migration.

So far we have regularly treated with the heterologous collagen 226 patients of both sexes, in hospital or in ambulatories, suffering from lower limbs vascular ulcers. Based on the pathogenesis, the ulcers were classified as phlebostatic (142), ischemic (66) and mixed (18). The ulcers were controlled every two days to check the eventual lysis of the collagen felt and partially or totally replace the sponge if destroyed by the lysosomal enzymes of the granulation tissue cells. In some cases a local antibiotic therapy was associated according to the antibiogram.

In our casuistry we achieved the complete healing of all phlebostatic ulcers and a faster improvement of the ischemic and mixed ulcers compared to standard therapy results. In three cases the treatment was discontinued due to the inadequate improvement of the haemodynamic situation and subsequent gram-negative infection.

The evaluation of the product efficacy was based on clinical parameters either subjective (pain, soreness, paresthesia and itch) and objective (entity of the exudate, periulcerus erythema, edema, granulation tissue).

In fig. 1-4 is shown a case of a mixed ulcer involving the whole leg circumference, which healed thanks to the regular application of heterologous collagen.

ooooo

Fig. 1

Mixed ulcer to the right leg

1-2 : medial side : beginning and end of treatment

3-4 : anterolateral side : beginning and end of treatment



1)



2)



3)



4)

DECUBITUS ULCERS IN BED-RIDDEN PATIENTS TREATMENT WITH HETEROLOGOUS LYOPHILIZED COLLAGEN

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Ageing implies involutive alteration processes: a reduction of the sebaceous mantle, modifications of the fundamental substance with degeneration of the collagen and elastic fibres, lowering of capillary net, ending nerves and tactile and painful hypoesthesia.

For these reasons the skin of elderly people is less resistant to microtraumas, particularly in the variation of external pressure that facilitates the onset of pressure ulcers.

A recent study has shown that after 20 days of stay in bed there is an occurrence of 7-8% of pressure sores: 50% of patients developing sores are over seventies.

Immobility is the highest risk factor and a necessary condition to their occurrence. Other factors contributing to this pathology: diseases reducing spontaneous movements, hypoalbuminemia or malnutrition in general, sphincteric incontinence.

Pressure ulcers are caused by: pressure, stretching force, friction, humidity.

The first one is widely spread out on the skin while in the subcutaneous layers and in muscles it is more concentrated: this is why the necrosis starts from the deeper layers while the skin is still undamaged. An ischemia takes place, followed by paralysis of the vessels, reactive hyperemia, edema due to passage of plasma from the interspace vessels with possibility of haemorrhages.

The vasal occlusion following prolonged external pressure makes the ischemia worse: metabolytes accumulate, the nutritional support decreases or is lacking, necrosis starts in the muscle fibres, in subcutaneous layers and subsequently in derm and epidermis.

On a normal mattress the decubitus provokes on bone prominences a pressure of 100-150 mmHg: the transcutaneous tension of O₂ drops to zero with no pathological effects if the exposition is not prolonged or repeated and stretching is not associated.

This mechanism occurs when the patient sitting on an armchair slides toward the lower part of the seat or, if staying in bed, toward the feet.

The rub is the superficial stretching of the skin caused by linen; the fourth important factor inducing superficial lesions is the humidity.

Patients confined in bed or sitting on an armchair must be repositioned at least every two hours: researches are being made about the damages provoked by the alternance of compression and decompression during repositioning (similar to those occurring in the pharmacological removal of obstructions of the coronaries).

In diabetic patients the skin and the skeletal muscle are characterized by a reduction of the maximum blood perfusion, due to microangiopathy.

In fact the formation of microaneurisms, the structural alternance of capillary loops, of small arteries and veins and the deposition of glycoproteins positive to PAS reaction as well as the thickening of the basal membrane sensibly slow down the oxygen passage.

The superimposition of pathogenous bacterial flora over the cutaneous lesions seriously compromises the tissue repair process: most frequent germs are Gram negative (*Proteus mirabilis*, *Escherichia Coli*, *Klebsiella*, *Pseudomonas Aeruginosa*) but also Gram positive (*Staphylococcus Aureus*, *Streptococcus*, *Enterococci*).

The degrees of the lesion can be evaluated as follows:

- **stage 1** : lesion of the epidermis
- **stage 2** : involvement of the derm
- **stage 3** : deep lesions, involving also the subcutaneous layers (may be covered by eschar)
- **stage 4** : extension to muscles or bones

The wide-spectrum antibiotic therapy is efficacious against Gram⁺, Gram⁻, and anaerobes; it is useful to previously perform a surgical debridement to remove the eschar.

Topical antibiotics did not show cytotoxicity: they must be used for short periods and discontinued when the lesion is cleansed.

Antiseptics based on hydrogen peroxide, sodium hypochlorite and iodine are histotoxic and can damage the tissue repair process.

Enzymes (collagenase, fibrinolysin, desoxyribonucleases) are useful to remove the necrotic tissues but damage the granulation tissue: they must be avoided when the lesion is cleansed.

In order to facilitate the healing process, after cleansing of the ulcer we used a collagen sponge.

A series of studies shows that this device has an haemostatic effect, a chemotactic action on platelets, monocytes and fibroblasts: the heterologous collagen favours the fibroblasts proliferation and acts as a modulator on the granulation tissue.

Periodic medications verify the status of the collagen unity previously applied since the time and mode of prosecution of the treatment varies depending on it.

Three possibilities may occur:

1) the collagen sponge is still in situ, integral, not imbibed of exudates, adherent to the bed of the lesion. In this case the collagen must remain on site, avoiding removal not to alter the stimulation to healing process;

2) the sponge is more or less lysed, with presence of more or less large fragments of collagen, adherent to the bed of the lesion or along its edges.

In this case new unities will be applied to replace those dissolved, avoiding to remove eventual residues of the previous ones;

3) the sponges of collagen are still on site, but saturated with exudates, not adhering to the bed of the lesion. It must be suspected a bacterial infection on the site of the lesion, favoured by an incomplete cleansing prior to collagen application. A bacteriological test must be performed and cleansing repeated, followed by a new application of collagen.

For this study we evaluated 46 patients, hospitalized in our "bed-ridden unit", affected by the following pathologies:

- 11 fractures (thigh bone, pelvis, kneecap)
- 10 diabetes mellitus
- 4 amputations (thigh, toe)
- 2 rheumatoid arthritis
- 3 bronchopneumonia
- 1 plastic surgery after extirpation of leg epithelioma
- 6 angiodermatitis
- 3 cardiac disorders
- 1 myeloma
- 4 varices to lower limbs
- 1 crio-globulinemy

Three patients went out the study because of death. Six patients died for various pathologies, but the observation time was enough to judge the efficacy of the treatment.

The age of patients ranges between 50 and 97 years, mean 82.5; 14 were males and 29 females.

The treatment lasted from a minimum of 30 to a maximum of 154 days with a mean of 61.4.

24 cases healed completely (55.81%); 11 gave a good response (25.58%); 8 a poor response (18.60%), out of which 5 sacral sores with a death after 30 days and one after 38 days.

The percentages of healing, referred to the stages were:

- stage 1 : 2 cases 2 healings (100%)
- stage 2 : 19 cases 14 healings (73.68%)
- stage 3 : 18 cases 8 healings (44.44%)
- stage 4 : 4 cases 0 healings (0%)

The poor responses were respectively:

- stage 1 : 2 cases no poor response (0%)
- stage 2 : 19 cases 1 poor response (5.26%)
- stage 3 : 18 cases 3 poor responses (16.66%)
- stage 4 : 4 cases 4 poor responses (100%)

A statistical analysis based on age, independently from general pathology and kind and site of the lesion, points out 68% of healings in the group between 50 and 75 years against a 43% in the group from 76 to 97 years.

Poor responses are 14% in the first group and 26% in the second one.

Herebelow a meaningful case (*see photos at the end of the report*)

M.C., 87 years old, female.

Diagnosis: angiodermitis of right foot, affected by rheumatoid arthritis and aorto myocardic sclerosis.

Since two years the patient presented a solution of continuity 7x4 cm; she was hospitalized various times in bedridden units and in dermatology and lately was treated with simple dressings to protect the lesion.

On the 21st May 1989 was performed disinfection with topical rifamycin and started the treatment with two products: lyophilized collagen on the proximal site and hydrocolloid on distal site.

This criteria was adopted for practicality, considering the size of the dressing, instead of performing a specular medication which would have required the fragmentation of products.

As from June 12, medications were renewed every two days and before them a wash with saline solution and repeated biopsies for culture, always negative, were also performed. The size of the lesion was controlled by direct measurement and a photographic evidence was taken weekly.

From the 12th June 1989 due to granulation of the edges and bottom of the lesion, the medications were renewed at three days interval; from the 18th July due to the more favourable results in the proximal site of the lesion, the comparison with hydrocolloid was discontinued and the medication was performed exclusively with collagen, twice per week.

On the 3rd October 1989 after 128 days of treatment, the lesion was almost completely reepithelialized and the patient asked to leave the hospital committing herself to continue the treatment at home.

At a later control the complete healing of the lesion was found.

As a conclusion to our study we wish to point out the following:

- 1) undoubtedly the collagen is useful in treatment of ulcers, regardless of their etiopathogenesis;
- 2) it is better an early treatment, since high percentages of recoveries and good results are remarkably higher when ulcers are treated in their early stage;
- 3) nevertheless also in advanced phases better results can be obtained compared to those achieved with other dressings or medications;
- 4) finally, it has to be noted the excellent tolerability of the product, the complete absence of side effects, either general or local.

21st May 1989 disinfection with topical rifamycin and beginning of treatment with two products: lyophilized collagen on the proximal site and hydrocolloid on distal site



Progression of healing



3rd October 1989 after 128 days of treatment, the lesion was almost completely reepithelialized



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THE USE OF LYOPHILIZED COLLAGEN IN GYNAECOLOGICAL SURGERY

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It is widely known that collagen plays an important physiologic role in the tissue repair process and healing of solutions of continuity of the skin and mucosa.

Our attention was mainly directed to those situations involving a loss of substance, such as myomectomy and "cup" type haemorrhages and in certain cases of uterine enucleation where the pericapsular vascular bed bleeds abundantly. We have also widely used the collagen in cystopexy and Kelly's hysteroplasty, when the sub-urethral muscular-membranous tissue offered a poor support in order to improve haemostasis and stimulate with a bridge of lyophilized fibrous tissue the formation of healing tissue to support the sub-urethral structures, thus restoring the frame and the urethro-vesical function.

As a whole 240 patients have been treated, aged between 25 and 75 years, hospitalized for conservative or destructive surgical operations from a variety of diseases.

We performed 92 laparotomies and 148 vaginal operations, with or without celiotomy.

The collagen, square pads 5x5 cm 0.5 cm thick, was used during surgery every time bleeding occurred with loss of substance, such as in simple or multiple myomectomy, in cases of laparohysterectomy with or without complementary adnexiectomy, in presence of bleeding areas due to detachment of adhering viscera or in case of microhemorrhages of the pelvic cellular tissue below the infundibulum pelvic vessels, or between the layers of the large ligament.

The collagen sponge was laid over the bleeding area before peritonizations, or else folded to fill the cavities resulting after myomectomy, in order to remodel the area where the loss of substance occurred. After cystopexy and Kelly's technique, the collagen was applied before the reconstruction of the vaginal wall.

In the 72 myomectomy the operation solved the symptomatology present before surgery. All subsequent controls gave satisfactory results from both gynaecological and echotomographic points of view.

Eleven patients who underwent surgery also for sterility problems were then successfully pregnant. In the only case of caesarean operation the scar of the previous myomectomy was not evident. In both vaginal and abdominal hysterectomies no relevant post-operative symptoms were recorded.

Tab. 1 - Causes of operations in which anallergic collagen was used

	Nr of cases
Incontinence	53
Cystocele	78
Different levels of utero/vaginal prolapse	40
Uterine sclerohypertrophy	97
Single or multiple fibromyomas in the body of uterus	44
Haemorrhagic metropathy	3
Pelvic endometriosis	13
Parauterine tumefactions	7
Ovarian cyst	9

Tab. 2 - Operations where anallergic collagen was used

	Nr of cases	Age (mean)	Days in hospital (mean)
Myomectomy	60	37	10
Laparohysterectomy	14	48	10
Colpohysterectomy with urethrocystopexy	118	55	8
Colpohysterectomy	27	56	8
Urethrocystopexy	18	42	8
Adnexectomy	25	42	8
	262	46.7	8.5

Tab 3 - Symptomatology before and after myomectomy treated with anallergic collagen

	Pelvic algia	Repeated metrorrhagia
Before the intervention	18	21
After the intervention	0	0

Tab. 4 - Symptomatology before and after colpohysterectomy and laparohysterectomy treated with anallergic collagen

	Before	After
Dysuria	16	2
Pervic-algias	14	0
Dysmenorrheas	3	0
Dyspareunia	3	0
Metrorrhagias	5	0

Tab. 5 Anallergic collagen

	Before	After
Urinary incontinence	105	10
Dysuria	50	16
Dyspareunia	20	0
Metrorrhagias	46	0
Pelvicalgias	17	0

Only in a few cases the patients claimed dysuria, most probably due to an implanted catheter. After the operation none of the symptoms previously claimed by the patients occurred.

All subsequent controls were satisfactory from both a gynaecological and an echotomographic point of view.

After repair surgery of vaginal prolapses out of the 125 patients previously suffering urinary incontinency only 10 claimed it. Some non-significant episodes of dysuria took place in particularly sensitive patients, caused by catheter, which disappeared in subsequent controls.

The most significant result however is the disappearance of urinary incontinence from effort in almost all the treated cases.

The lyophilized collagen proved to be very handy, useful, well tolerated and effective in its topical use in gynaecologic surgery.

In all patients treated no variations of blood values, nor immediate or late disturbances were recorded.

In all cases healing was satisfactory, as documented by the clinical course and subsequent echotomographic controls.

The disappearance of the urinary incontinence in almost all the cases of cystourethropexy is particularly interesting: it is like that collagen contributed to the consolidation of the suburethral floor, thus making the operation more effective and the result more satisfactory.

We can consider the results encouraging for the use of lyophilized collagen in the above cases and welcome enlarging its use in other gynaecologic surgery applications.

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THE HAEMOSTATIC ACTION OF HETEROLOGOUS COLLAGEN IN VASCULAR SURGERY

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Seeking a correct haemostasis in surgery and particularly in vascular sutures puts the surgeon in the condition to use methods, drugs and various products to achieve the best results and face safely the haemorrhage.

In my long experience as vascular surgeon the haemostasis has always been at the centre of attention along with prevention of infections, both present in every operation and possible cause of severe complications and therefore both to be fought with all suitable means and techniques. In the last years I could utilize in surgery, as haemostat for topical use, the heterologous lyophilized collagen.

Before that, I had been using various compounds as haemostats and could evaluate for each of them the positive and negative components not only in terms of technical results but also of side effects and treatment costs.

During the Istanbul Congress in 1990 I described the various methods so far followed, pointing out the characteristics of each of the products used as topical haemostats. Before starting the use of heterologous lyophilized collagen as vascular haemostat, I had been using a kind of microfibrillar collagen that however proved to be of difficult application and highly expensive.

Having decided to leave in situ the material under test whilst initially it was removed after haemostasis, it was necessary to verify if the collagen could cause intolerance even knowing its complete organic tolerability from previous experiences on a remarkable number of cases (use as vascular prosthesis in Dracon impregnated with collagen).

To support this guarantee of tolerability, for more than one year the patients who received collagen underwent various immunological tests including the dosage of the complement and of the circulating immunocomplexes, lymphocytic functionality and delayed hypersensitivity through patch tests.

None of the various patients who underwent operation and retained the collagen as haemostat showed primitive or secondary intolerance nor signs of immediate or late immune response.

The collagen was used experimentally in a rigorous way on over 200 patients and in different surgeries for a little more than one year.

The report submitted during the Istanbul Congress (162 patients) proves not only that the product has a good haemostatic activity but also that it does not induce side effects nor immunological phenomena. Therefore it has been decided to enlarge its application also to diabetic and hypertensive subjects.



Use of collagen pads in vascular surgery

As a result the heterologous collagen became of daily use in our vascular surgery division, as shown in the papers related to the Istanbul Congress.

The increasing familiarity achieved in the use of collagen convinced us that it could be utilized not only for arterial and venous haemorrhages but also in correspondence to inguinal regions where the risk and danger of lymphorrhea may provoke severe infections.

The application of collagen when suturing inguinal wounds in the numerous cases treated enlarges its field of application and I can guarantee that it is really helpful in avoiding lymphorrhea in inguinal area.

We can therefore conclude, after years of use, that collagen proves to be of high usefulness in reducing haemorrhages in surgery and in the vascular surgery sutures. Haemostasis is improved and accelerated, above all where bleeding is heavy, avoiding the use of other haemostatic methods and surgical actions too often more dangerous than useful.

The absence of side effects is an additional safety guarantee for the vascular surgeon.

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IMMUNOLOGIC EVALUATION

IN PATIENTS WITH GYNAECOLOGIC BENIGN PATHOLOGY WHO UNDERWENT SURGERY AND APPLICATION OF HETEROLOGOUS COLLAGEN

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The use of highly purified collagen is more and more frequent in various surgical applications. The use of an heterologous material - even if highly purified like type I collagen, acid insoluble, extracted from Achilles tendon with a non denaturing process - leaves the problem of the possible immune responses eventually inducible in the patient.

The study of this aspect is significant also for the importance that the immune system may get due to the deposition of collagen. It is well known in fact that the lymphocyte system through the production of interferon can influence the activity of fibroblasts. The aim of our work was to show possible modifications of the immune system induced by the application of an heterologous collagen in patients who underwent a surgery for benign gynaecologic pathology.

20 female patients (39-60 years old) underwent this clinical study, testing the blood before, 10 and 30 days after benign gynaecological surgical procedures.

In tables 1 and 2 are shown the monoclonal antibodies used and the lymphocyte stimulation test mode.

The evaluation of the lymphocyte underpopulations was performed by cytofluorimetric analysis.

All the patients during the pre-operative period had normal levels of all the lymphocyte subpopulations considered. No significant differences appeared in the responses of peripheral lymphocytes to PHA, ConA and PWM after the treatment with purified collagen.

None of the patients showed side effects depending on the treatment.

After treatment, no modification occurred in the studied parameters.

From the data available it appears that the application of heterologous collagen in the tested conditions is free from undesired immune effects.

Table 1

Lymphocytary underpopulation	
Antibody	Specificity
Leu 5b	CD 2
Leu 12	CD 19
Leu 4	CD 3
Leu 3a	CD 4
Leu 2a	CD 8
Leu 19	CD 5
Anti IL-2-R	CD 25
Leu 11a	CD 16
Anti Human HLA-DR	-
B 4	-

Table 2

Lymphocyte stimulation test mode on whole blood at 72 hours	
Stimulation (mytogen)	Concentration
PHA	140.0 J4/ml
ConA	5.0 µg / ml
PWM	2.5 µg / ml

HETEROLOGOUS LYOPHILIZED COLLAGEN

In the treatment of phlebostatic ulcers

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The chronic venous insufficiency (CVI) and its most severe clinical manifestation, the phlebostatic ulcer, are consequences of the orthostatic venous hypertension, of its scarce orthodynamic decrease and - above all - of the incidence of these macrocirculatory haemodynamic forces on the microcirculatory haemodynamics.

In particular, Widmer's stage III is characterized by a high orthostatic venous pressure both in the superficial and deep venous systems, by a reduced orthodynamic pressure decrease and a significant venous and capillary stasis (1,2).

The CVI therapy must aim to reduce venous hypertension, stasis and its cellular effects, to activate the endothelial and tissue fibrinolysis, to reduce the stasis hypoxia. These goals are achieved with a personalized elastic bandage and an adequate pharmacological therapy (activators of fibrinolysis).

This therapy is usually sufficient to activate a good tissue repair process; however, especially in the inveterate or badly treated ulcers it is advisable the topical use of fibrinolytics by intramesodermic and intraulcerous way (3), which strongly stimulate the granulation process.

Collagen represents a physiological substrate to the final tissue repair process.

Based on these conditions, validated in various clinical studies (4,5,6,7), we aimed to evaluate, apart the therapeutic efficacy of topical collagen particularly as to healing time, the mechanism of action as shown from histologic examinations.

For ethical reasons (the therapeutic strategy of phlebostatic ulcers is already widely known), the study was performed on a limited number of cases, with ulcers treated unsuccessfully since long.

Five patients affected by CVI from post-thrombotic syndrome, all at stage 3 of Widmer, with ulcerative perimalleolar lesions dated from a minimum of 6 to a maximum of 24 months which never healed even temporarily, received orally heparan sulfate and a collagen topical medication, renewed every 48 hours (the fibrinolytic intramesodermic treatment was not performed to allow a more genuine evaluation of the topical collagen therapy).

At the beginning of the treatment and when the size of the ulcer was 1/3 of the initial value, a biopsy was performed for histological control.

The collagen treatment was well tolerated by all patients, without any local or general allergic reaction; the sizes of the ulcers were reduced by 2/3 compared to their initial value in a time between 20 and 50 days except case IV who, at the 15th day, showed a mycotic overinfection (topical treatment associated with phenic fucsin 0.3%) which doubled the healing time (Tab 1)

TABLE 1 : case history and results

Case Nr.	Age	Diagnosis	Ulcer's age	1/3 initial size	Healing
		(*)	(months)	(days)	(days)
I C.F.	70	PTS	8	20	30
II F.P.	69	PTS	24	38	50
III	67	PTS	6	49	60
IV	62	PTS	20	100	140
V	63	PTS	24	36	57

(*) PTS = post-thrombotic syndrome

TABLE 2 : pain modifications

Observation time (days)	SCORE				
	4	3	2	1	0
0	I - III - IV	V	II		
8	IV	III - V	I	II	
15		IV	III - V	I - II	
22		IV		III - V	I - II
29			IV	III - V	I - II
36				III - IV	I - II - V

Score 0 : absent

1 : low

2 : intense

3 : much intense

4 : requiring analgesics

Pain was reduced by the treatment; the use of analgesics, at 0 time needed by three patients, was necessary in only one case at the 8th day (this was still case IV, which obviously falls within the so called "persistent ulcers"); at the 15th day none of the patients showed pain; at the 29th day pain was intense in one patient only, low in two and absent in other two; at the 36th day pain was low in two patients and absent in three (Tab. 2).

The clinical healing, obtained in a time variable between 30 and 60 days (Tab.1), was satisfactory in all cases with good scars and all the patients resumed their physical activity (Fig. 1, A-B-C).

Fig. 1 A



Fig 1 B



Fig. 1 C



From histological point of view the main aspects to be noted were the intense presence of lymphoplasma cell infiltrate and fibrinoid pericapillary necrosis, with endothelial swelling phenomena in the initial biopsy and the repair in vascular fibrotic areas regularly ordered, surrounded by tissular segments richly vascularized at a later control.

Our observations although based on a limited number of cases led to the following conclusions:

- a) the therapy of phlebostatic ulcers cannot be limited to topical treatment but must necessarily correct all the physiopathologic alterations leading to its formation;
- b) the clinical validity of the use of topical collagen in the treatment of phlebostatic ulcers is confirmed;
- c) the histological characteristics of the healing process, with the presence of richly vascularized tissue segments and orderly connectival fibrous reaction, testify the role of inducing substrate performed by the collagen and represent a valid guarantee for the stability and duration of the tissue repair.

In our opinion, in younger ulcers promptly treated following our protocol, a prevalence of neo-vascularization phenomena toward the fibrotic ones may take place, thus obtaining a more physiologic repair and possibly a total reepithelialization.

We can therefore conclude that the topical use of collagen in the treatment of phlebostatic ulcers is surely indicated for long persisting lesions, but can find application also in recent lesions where the "healing time", for its social and economic repercussions, represents an additional advantage in its use.

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THE ROLE OF HETEROLOGOUS COLLAGEN IN THE HEALING OF RESIDUAL POST-OPERATIVE CAVITIES

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The recent acquisitions on the cytologic and biochemical aspects of the tissue regeneration and tissue repair led to valorize the role of collagen in the healing processes (*David and Berfield, Tooke, Clark*).

From 1986 to 1991, at the First Chair of Surgical Anatomy and Surgery Courses of the University of Catania we observed 96 cases of pilonidal fistulas.

Twenty-one patients healed for primary closure and 75 for secondary intention. Twenty-six patients were treated with pads of lyophilized heterologous collagen.

After the sinus excision and the closure of the residual sacrococcygeal cavity to reach haemostasis, same was re-opened on fourth day. After 12-24 days and complete cleansing of the cavity and formation of granulation tissue, some collagen pads were laid on the granulating bed of the lesion to form a uniform layer and then covered with a compressive bandage. These medications were repeated on alternate days until complete healing.

After 48 hours from previous medication the collagen sponge was no more macroscopically recognizable being embedded in the fibrino-haemorrhagic layer, fully undistinguishable from the surrounding granulation tissue except the peripheral parts due to a pale pink colour compared to nearby tissues.

This implied a reduction of the residual cavity at an extent almost corresponding to the thickness of the pad used. The scarification of the surface covered by the collagen provoked a "cup" type haemorrhage, showing its incorporation in a very vascularized granulation tissue. The subsequent medications on alternate days showed even better the evolution of this phenomenon.

According to the entity and rapidity of these processes, variable from patient to patient, the pads were applied one every 3-5 days.

The histological control of the granulation tissue, performed in 9 patients 48 hours after the last application of collagen, evidenced the complete dissolution of the collagen pad itself and an intense granulation with lympho-plasma-cell and granulocytic infiltrates.

In conclusion the excision of pilonidal fistulas, with secondary healing, although offering higher success possibilities (*relapse rate 0-12% - Akawari, Al-Hassan and Coll., Azab and Coll.*) sometimes protracts, even remarkably, the healing time.

Our 21 patients who healed by primary closure showed a healing time of 12 ± 3.99 days, with a 23% relapse rate. The 49 patients who healed by secondary closure showed longer healing time, between 2-4 months, with a 0% relapse rate.

In the 26 cases who healed by secondary closure with application of collagen, the healing time was remarkably reduced, between 5 weeks and 2 months with no relapses.

From 1986 to 1991 we performed rectum resection for carcinoma on 39 patients aged between 43 and 77 years. The healing of the residual cavity occurred on 19 patients by primary closure; in 11 cases the cavity had to be reopened whilst in 9 cases we got secondary healing.

The patients who underwent the reopening of the cavity due to a suppurative process (11 cases) were treated daily with repeated washes of the residual cavity during 15-20 days. Only after complete cleansing of the cavity and growth of granulation tissue, we treated 4 patients with applications of collagen pads kept with a compressive bandage. These medications were repeated every other day until complete healing. According to the entity and speed of these processes the pads were applied one every 3-7 days. Three of the 9 patients who healed by secondary closure were treated with collagen pads, as an average 10-14 days after surgery.

The patients who underwent the reopening of the residual cavity and were medicated without collagen (7 cases) healed in a range of time between 3 and 5 months; those treated with collagen (4 cases) healed after 2-3 months.

Among the patients who healed by secondary closure, medicated without collagen (6 cases), the healing time was ranging between 2-4 months, whilst those treated with collagen healed after 1,5-2 months.

Therefore the suppuration of the residual cavity - requiring the complete cleansing of the abscess - significantly protracted the healing time. The complete control of sepsis allowed a fast repair of the loss of substance, favoured by the application of collagen pads. On the other hand, in the patients who healed by secondary closure the absence of suppurative processes favoured a faster granulation, accelerated by the use of collagen (Fig. 1-2 and 3).

It must be noted however that the regeneration and repair processes are strongly influenced not only by local factors connected to the cleansing of the residual cavity, but also by general parameters such as age, anaemia and malnutrition, whose correction is essential to the success of the local treatment.

Finally, the healing of large post-operative losses of substance is favoured by the application of heterologous collagen, with a remarkable reduction of the repair time. The cleansing of the cavity and the application of the collagen on a well granulating tissue are essential local conditions to the success of the treatment. This requires a free interval between surgery and beginning of treatment, variable from person to person, depending on the evolution of the residual cavity, on the speed and intensity of the granulation process and on the eventual presence of previous or superimposed infections.

This hinders the formulation of precise terms on the beginning of the treatment, whose evaluation is mainly clinical. However once the application of collagen is started, both in case of pilonidal sinus and post-rectotomy cavity, a significant reduction of healing time is recorded, thus demonstrating clinically the efficacy of the use of heterologous collagen in the healing of post-operative cavities.

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Fig. 1

Healing by second intention of the residual perineal cavity after rectotomy. Aspect of the cavity, already granulating on the 20th post-operative day

**Fig. 2**

Residual cavity after rectotomy. 30th post-operative day. The collagen pad, 24 hours after its application is already incorporated in the tissue, where is still recognizable.

**Fig. 3**

Same case shown in fig. 2. After 48 hours the collagen is no more recognizable unless for the pale pink colour on the bottom of the cavity where it was applied.



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HETEROLOGOUS COLLAGEN

Intra-operative use in vertebral surgery

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Several biological and clinical experiences have pointed out since long the haemostatic and healing roles of collagen and its stimulation of granulation and cicatrization tissue growth.

These actions have been exploited both in intra-operative surgical haemostasis and in the treatment of tissue lesions of different etiology.

We use the sponges of heterologous collagen in lumbar and cervical vertebral surgery both as haemostats and wound healers.

As to the lumbar tract, in the treatment of disk prolapse through laminectomy and discectomy, after removal of the diskal material we apply a collagen sponge in contact with the laminotomy area.

Also in large decompressive laminectomies, during the treatment of tight vertebral stenosis, we place various sponges of collagen in the excision, in contact with the dural sack.

A good haemostatic action has been noticed during surgery, allowing to prevent post-operative haematomas.

As to the cervical rachis we use the collagen during surgery for disk prolapses and myelopathic syndromes caused by arthrosic osteophyte compression.

In the first case we perform a frontal herniectomy according to Robinson, followed by arthrodesis with implant taken from the iliac crest.

Collagen is applied in the exposed dural sack in contact with its surface, in correspondence to the disk space explored before positioning of the intersomatic bone implant. Then we applied other collagen sponges on the vertebral surface as haemostat before the closure.

The surgical treatment of myelopathic syndromes from osteophyte compression, caused by back compression, varies according to the interested levels. In case of simple level a transdiskal osteophylectomy and an intersomatic arthrodesis are performed, similarly to the treatment of disk prolapse. The mode of use of collagen is therefore the same.

In case of multiple levels and when cervical lordosis is not maintained, the above intervention is performed again at the interested levels.

Whenever levels are contiguous the arthrodesis may be performed with a single bone implant, in which case we place the collagen between the dural sack and the implant along all its extension.

If the cervical lordosis is maintained we perform a decompressive laminectomy in the back, with a "cord effect" on the marrow which moves backward. In this case we place the collagen on the exposed dural sack.

Based on the two main actions displayed by the collagen (haemostatic and wound-healing) the following remarks are made.

It is doubtless the importance of the haemostatic action of collagen in this type of surgery where one of the early complications may be represented by haematomas.

Furthermore, collagen displays a double prophylactic action on peridural cicatricial fibrosis, responsible of late compressive relapses. This fibrosis may in fact derive partly from the haematoma (here again the importance of the haemostatic action) and partly from cicatricial phenomena.

The collagen in contact with the dural sack as above described forms a biological barrier leading to an ordered cicatricial disposition, exactly as it happens at dermal-epidermal level, and then is totally reabsorbed. This was partly confirmed by the low number of post-operative peridural fibrosis evidenced by TC and RMN controls, and partly by the finding of ordered recognizable cleavage planes during late new interventions on rachis treated for disk prolapses at contiguous levels.

The high biocompatibility of the heterologous collagen guarantees a safe use, free from any type of side effect or complication; its complete reabsorption allows in wide laminectomies for vertebral stenosis an additional back extension of the marrow in the long run, increasing the "cord effect" looked for in Aboulker intervention.

It is therefore clear that apart for its haemostatic action, the heterologous collagen can be used in vertebral surgery also for its specific biological characteristics.

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Fig. 1
Antero-trans-diskal cervical herniectomy;
intersomatic arthrodesis according to
Robinson
The collagen sponge is placed on the dural
sack before implant.

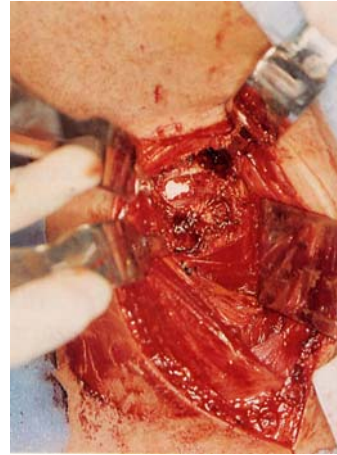


Fig. 2
The same case: positioning of the collagen
before the closure.

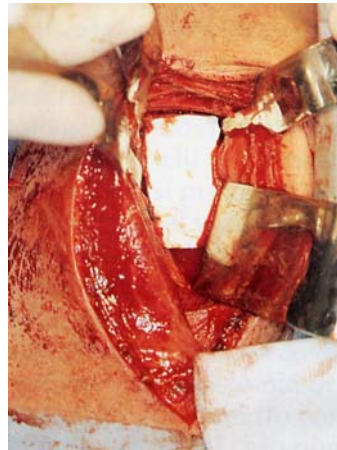
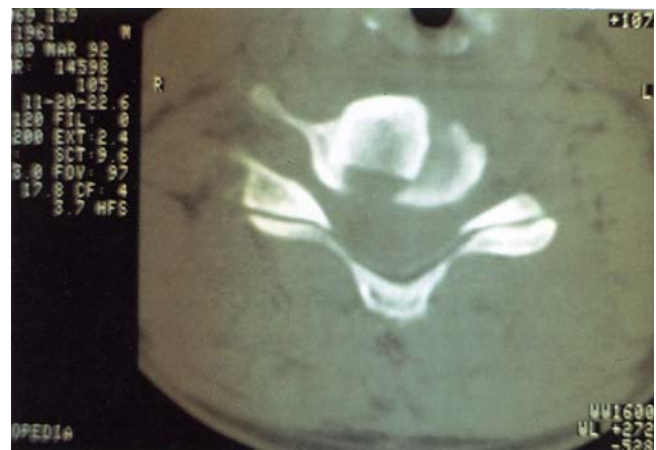


Fig. 3-4
TC and RMN controls, not evidencing
residual fibrotic-cicatrical phenomena, 2
years after the intervention



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