THE BURN DISEASE: A DISEASE OF GREAT VALUE IN THE CULTURAL HERITAGE OF PLASTIC SURGERY

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Personal introduction
In 1961 I began my career as a plastic surgeon at the Department of Plastic Surgery of the Civic Hospital of Padua. In those years, the department was headed by its founder, Prof. G. Dogo, who had just gained his independence to work within the discipline of surgery. Its key feature consisted, at its core, in an entirely new section for those times: the Burn Centre, later known as the “Intensive Care Unit for Acute Burn Victims.” At that time, Prof. Masellis, the founder of the Mediterranean Burn Club, was also working among us.

The department was still dealing with the disastrous traumatic pathologies that the Italian population had from the Second World War. The beds were still largely occupied by patients suffering from war injuries caused by bomb explosions and fires. These were the reason for the creation of the Burn Centre and subsequently for the promotion of the establishment of a department of plastic surgery. I therefore had the opportunity to see a multitude of different clinical cases and to experiment with the various operation techniques known to plastic surgeons at the time. But it was not only the surgical aspect that fascinated me: I was fascinated by the burn as a disease – the extraordinary problems of their pathophysiology and the logic of treating them, generally and locally – no longer as had been suggested by vague suppositions, but by suggestive hypotheses based on clinical and experimental observations. Over the years, the skills involved in plastic surgery have expanded: its numerous therapeutic procedures have been applied to the treatment of many other diseases. But the burn-as-disease was always at the top of my cultural interests. It always had something to teach me, whether clinically, scientifically or ethically. Yes, even ethically, because the burn patient, like few others who are ill, truly challenges his physician’s ethical core and moral strength.

The contents of this piece of writing stem from “opinions” that the author has had in the practice of his profession while “listening and reading” everything that has happened to him during his work as a plastic surgeon over half a century. These opinions formed bit by bit; only now am I attempting to verify and justify them, intentionally seeking the bibliographic testimony and opinions of others.

Introduction
I have always considered the burn-as-disease to be the spearhead of the plastic surgeon’s cultural heritage. Over the course of my 50 years of medical practice I was able to follow the progress in this field close up, and increasingly appreciate the immense contribution that its basic concepts and their development over time have provided to the body of biomedical knowledge. Observations, insights and/or hypotheses have indeed given positive responses to problems which are inherent to burn care, but have also shed light on diseases which did not appear to have any relation to burns. In discussions at medical school we always called these “pilot observations.” They have to do with:
1. Secondary shock,
2. Hypercatabolic reactions,
3. Rejection of homologous tissues and organs,
4. Myofibroblasts,
5. So-called piloted healing and surgical induction.

Much has been written about burns, since antiquity – but it was only in 1797 that medical science began to consider them “scientifically.” In John Kentish’s “An Essay on Burns,” published in London in 1797, the author explicitly stated (on the long title-page) his desire to discuss the issue of “tending to rescue the healing art from empiricism, and to reduce it to established laws”. In spite of this, up to the beginning of the twentieth century the burn-as-disease was seen exclusively as a disease of the skin, with its own particular problems – to be treated solely as a skin disease and nothing more.

Secondary shock
The identification of the pathogenesis of the shock within a burn, the secondary shock, is the most significant pilot observation.

The impressive drop in cardiovascular function that occurs immediately after an extensive burn has been stigmatized as the inevitable and typical fate of the disease (when it is at high temperatures). In the past it was called, very generically, “cardiovascular collapse”. With the ad-
vance of Anglo-Saxon literature on the international scientific scene, the condition became known as “shock.” This term designated a syndrome of “peripheral vascular failure” caused by a violent event: a severe injury, a profuse hemorrhage, an infection, and so on. In the early decades of the twentieth century, some similarities with the clinical conditions of the aforementioned critical situation were identified, and common pathogenetic mechanisms were believed to exist, but only hypotheses about their nature were ever formulated.

The first pathogenetic insight had to do with shock from burns. This story begins with Underhill and takes place in the U.S.A.

F.P. Underhill was a professor of pharmacology at Yale University. He had the opportunity to follow the care of the 20 victims of the Rialto Theater fire in New Haven in 1921. He studied the trends of hematocrit, serum hemoglobin and sodium, estimated fluid loss and analyzed the contents of the vesicles. He was thus able to identify the significance of the loss of the liquid and protein components of the blood in the burn area, and of the resulting depletion of the bloodstream.

Cope and Moore subsequently developed the concept of the burn edema and confirmed the hypothesis with the ex juvantibus experience: they proposed an initial formula of infusion therapy in relation to the severity of the disease, which proved to be quite effective. Their experience resulted from a fire disaster as well – the 1942 Coconut Grove catastrophe.

Their formula later underwent considerable changes in relation to new discoveries that were taking place: Moyrer, Margraf and Monafo, Moylan and co., Artuson, Monafo and others. Burn shock was attributed to hypovolemia. It was understood that the initial mechanism for this was the leaking of fluid in the affected area due to an inflammatory serous reaction, and the quantitative relationship between the extent of the damage and the extent of the leakage was recognized. While very high in the early hours, it is progressively reduced in close relation to the reduction of the magnitude of the edema fluid-swelling process.

In 1965 Cotran et al., along with colleagues G. Majno and E. Palade of Boston, were able to demonstrate the validity of the assumptions previously formulated, with experimental burns on rats and using an electron microscope and the injection of a suspension of colloidal carbon. It could be assumed with sufficient certainty that in the tissues of recently burned patients, holes apparently determined by the changing shape of the endothelial cells (which went from being flat to globular) were forming in the walls of small blood vessels. With this change reciprocal contact is lost, and therefore also the continuity of the wall. Between one cell and another a crevice (stoma) is formed through which the water, along with molecules up to a certain size, can escape. This is believed to be the site of leakage. Only when the integrity of the wall is re-established (which normally takes place within 24-36 hours) in conjunction with the recanalization of the lymphatic capillaries, losses cease and edema absorption begins. Thus the concept of “replacement therapy” originated, a treatment quantitatively equivalent to losses.

The great wars of the 20th century gave physicians (whether military or not) an unparalleled opportunity to get firsthand experience dealing with burns. And it was in the lines of fire of the last world war that the Pyrogram (Fig. 1) came into being – a table that was easy to use and portable in the pockets of camouflage uniforms, which indicated the quantity of liquid to be injected in the first 48 hours along with the type of liquid and the rate of injection, comparing the % of surface area burned to the patient’s body weight.

These observations in the field of burns shed much light on the pathogenesis of all other syndromes of high criticality, and shock acquired its current pathophysiological connotation: it was understood as a syndrome of peripheral vascular insufficiency due to progressive deterioration of microcirculation, i.e. of that part of the vascular apparatus lying beyond the arteriole structure, and known by the name of terminal vascular district, or even more generally, as capillary circulation: it has gradually come to be recognized as the physiopathological base common to all diseases that lead to shock.

The contribution of burn treatment and study to the body of knowledge regarding the many symptoms that can lead to thermal trauma did not stop there. The general interpretation of the disease has changed in recent years. Based on observations of the ultrastructural or even molecular variety, we tend to identify the mechanism that underlies all clinical conditions so far interpreted as complications (sepsis, cachexia, ileus, shock lung, etc.) as being part of the so-called systemic inflammatory response. Therein we can see the hidden “common thread” that binds the various symptoms and manifestations in a progressively broadening continuum which correlates to the factors of seriousness of the condition in question. This continuum, in the most extreme cases, begins with shock and ends with the collapse of all organs, following a developmental process that can quickly expand pell-mell, according to an order that has been predetermined in many ways. This systemic inflammatory response is observed in burns classified above a given criticality. The clinical syndrome that results is defined as systemic inflammatory response syndrome.

It has been observed that even this process is not exclusive to the burn-as-disease; it is common to all the conditions in which there is a marked destruction of tissue (ischemia-reperfusion, pancreatitis, multiple trauma, etc). The response is mediated by inflammatory cytokines released
Fig. 1 - The Pyrogram that doctors on the front lines in World War II used. Sliding the card according to the patient’s weight and the percentage of their burns, it indicated the amount of liquids that should be injected or applied during the first and second 24 hours, considering the formula in use at the time, the use of which was backed by Wallace.
during tissue damage: 1) TNF-α, released within minutes of trauma, 2) IL-1, 3) IL-6 and 4) interferon-gamma. The cells responsible for their release appear to be macrophages.\(^\text{11}\)

If the lesion is small, the amount of cytokines that are released is limited, the inflammatory response remains restricted to the damaged area, and it is followed by damage repair. If the damage is extensive and exceeds a given threshold, the number of mediators is high and the feedback and control mechanisms go into crisis mode. The mediators go around in circles and the inflammatory response becomes systemic. Many of these factors have been identified in the equivalent syndromes, contributing to the understanding of their pathogeneses.

**Hypercatabolic syndrome**

In addition to fostering improved understanding of the nature and mechanisms of the hypercatabolic reaction that all serious trauma injuries involve, regardless of their type, burns have contributed substantially to the field in recent years. The prestigious Brooke Army Hospital, home of the Army Burn Center, was the epicenter of research on this field.

When a severe burn patient overcomes the dramatic events of the initial phase of the illness, he enters the *dystrophy* phase, characterized by weight loss which is usually associated with anemia and hypoproteinemia.

Over the past twenty years, many strides have been made in the understanding of the metabolic problems that the burn patient faces during the illness.\(^\text{36,37}\) The progressive malnutrition that leads quickly to cachexia seems to be the outward manifestation of the so-called “metabolic response to trauma”, which starts on the fifth day about and lasts for some weeks. It is characterized by a marked movement toward catabolism (“catabolic reaction”), and in the untreated patient, leads to a negative nitrogen balance. The fall in body weight continues, accompanied by an increase in temperature and in cardiocirculatory rate (tachycardia), and associated with an increase in oxygen and glucose consumption, carbon dioxide production, glycogenolysis, proteolysis, and lipolysis. If these events are not quickly curbed by the appropriate nutritional therapy, the patient undergoes the erosion of lean body mass, muscle weakness, immunosuppression and depletion of repair capabilities. The size and duration of these depends on the severity of the damage and the therapeutic measures that are taken to combat it. Only when tissue loss has been almost completely repaired will the catabolic reaction stop.

At the center of this response, an alteration of the hormonal balance was identified. The temperature and humidity of the surrounding environment influence this, but do not cause it: it is temperature-sensitive, but not temperature-dependent. The burn patient is “warm inside”: his base metabolism is increased and his internal temperature can be 1-2 ° C above normal.\(^\text{40,41}\) The nervous system also plays its part with various mechanisms, which the thalamus and the hypothalamus are involved in.

It has been noted that this altered metabolic structure is not exclusive to severe burn disease. It has been identified in all stress syndromes and is today considered a general nonspecific reaction to a critical condition. The burn continues to serve as a field of physiopathological study that is very revealing and significant, especially for biochemists. The hormonal structure has undergone an important change: the hormones recognized as catabolic tend to prevail over those which are anabolic.

**Rejection of homologous tissues**

The study of experimental burns in animals, in the manner prescribed by the various research models, was of fundamental importance not only for the advancement of knowledge about the mechanisms that are fundamental to the healing process of a complex soft tissue lesion, or about the mechanisms of engraftment of autologous grafts; it was also successfully applied to the study of the principles of rejection of *homologous material*. It was the burn patient who gave Gibson and Medawar the opportunity to hypothesize that the rejection was immunological.\(^\text{11}\)

During the Second World War a young woman with extensive burns came to Glasgow Royal Infirmary. Despite the severity of her injuries, all third-degree, she survived the initial phase of stress and toward the thirtieth day her scabs fell off to expose richly vascularized granulation tissue. She was taken care of by two outstanding physicians: a plastic surgeon of the highest degree, T. Gibson, and pathologist P.B. Medawar (Fig. 2). In the absence of sufficiently large areas of healthy skin, used as donor areas, part of the pinch-grafts were taken from the patient’s brother’s skin. By the 15th day no difference could be noticed between the pinch-grafts of different origins: those which were homologous appeared to have taken root just as well as the autologous ones. Continuing on the exposed surface, granulating, on the same day a second series of pinch-graft counterparts were applied, again taken from the aforementioned donor. Some extremely accurate histological analyses pointed out an extraordinarily interesting behavior. After a fortnight, during which the homologous grafts of the first series were indistinguishable from the autologous ones - that is, they had perfectly taken root - they began to show signs of distress. The epidermal cells were swollen and were colored less intensely, on the edges they were peeling off, and the quality of the infiltration was modified: histiocytes and plasma cells were becoming more and more numerous. On the 23rd day the first series’ homologous grafts were in disrepair. It was
Fig. 2 - The article, published in the Journal of Anatomy in 1943, in which Gibson and Medawar announced the immune nature of the rejection of homologous tissues on the basis of clinical observation carried out on a burned child. (T. Gibson and PB Medawar: The fate of skin homografts in man. J. Anat., 77: 299, 1943).
furthermore surprising to observe the behavior of the second series’ pinch-grafts, implanted 15 days afterward: in these the engraftment, as observed in the first, absolutely did not happen and the process went directly to the dissolution phase. Their histological appearance on the tenth day was identical to that of the first series’ grafts on their 23rd day. In this behavior, the immunological mechanism of rejection was supposed. The first set of pinch grafts sensitized the host and prepared for a general reaction that immediately led to the rejection of any and all biological material coming from the same donor. Medawar cherished this detail and further developed it in the laboratory. Aided by prestigious collaborators, he confirmed the validity of the hypothesis of immune rejection in transplants in general, and discovered the phenomenon of artificially-induced tolerance and runt disease. In 1960 he was awarded the Nobel Prize, along with Frank MacFarlane Burnet. The observation of a burn patient had triggered an extraordinary chain of biological insights that would lead to equally extraordinary practical benefits in the field of organ transplantation. Immunological hypotheses on the origin of intolerance of homologous tissues in the exchange between individuals of the same species had already been made, but were still a bit confusing and not at all substantiated by experimental observation.

The era of organ transplantation had begun. Its subsequent clinical and scientific achievements require no comment. As for general surgery, the sky was the limit.

More difficult was the field of tissue homografts. Fortunately today skin, bone, cartilage, nerves, tendons, etc., taken from cadavers and preserved in Tissue Banks, are available for all types of specialized surgeries.

Myofibroblasts

Plastic surgeons dedicated hundreds of clinical and laboratory research projects to the problem of post-burn scar retraction. Granulation tissue gave the opportunity to observe things that would be widely applicable to many diseases. It also gave the inspiration for new interpretations of the after-effects of common internistic diseases. In fact, in our discipline they have acquired a prominent role both in doctrine and in practice; according to current views, myofibroblasts are the main actors in tissue healing, scar retraction and scar deformity. They are therefore the critical link in the pathophysiology of diseases which the plastic surgeon most often has to deal with.

The problem of wound contraction had long tormented the minds of clinicians and researchers. In ‘71 and ‘72 came the first observations from the School of Geneva (Gabbiani, Majno et al.) : a fragment of granulation tissue was contracted in vitro and some of its cells presented some filaments in the cytoplasm which were identical to those that can be observed within smooth muscle cells. This contraction was influenced (or enhanced or inhibited) in the same way by drugs that affect the contraction of smooth muscle cells: bradykinin, histamine, angiotensin, vasopressin, epinephrine, papaverine, acetylcholine, serotonin, and others. \(^{24-41}\) Immunohistochemistry and electron microscopy revealed in the samples the presence of modified fibroblasts, meaning fibroblasts that possess characteristics suitable to justify the contraction of the fragment. Streaks were noticed in their cytoplasm which were colored in the same way as the fibrils of smooth muscle cells and may have been responsible for the contraction: they were thus defined stress fibres, and the cells were called myofibroblasts. They appeared to be fibroblasts modified by having taken on a system of filaments within the cytoplasm which, as could soon be detected, were made of actin, a typical protein of muscle cells, which in cooperation with myosin constitutes the basis of the contraction.

As often happens in biology, when an investigation is broadened the problem becomes more complicated. In fact it soon became obvious that the cellular entity “myofibroblast” had no clear boundaries neither in form nor function: it could not be found only in the granulation tissue, nor derived exclusively from fibroblasts. Other cells with intermediate properties have gradually been identified and described.

At first, the myofibroblasts were deemed to be cells specific to “pathological” healing, with a precise derivation from fibroblasts. Subsequent observations revealed that completely identical cells were present in many other pathological conditions characterized by retractive phenomena: in Dupuytren’s palmar fibromatosis, in stenosing synovitis (De Quervain’s disease – trigger finger), scleroderma, in the periprosthetic capsule and in many of the fibroses which affect deep organs such as the liver, the kidney, the lung and the heart. They were even found in a pathological condition that apparently shows no signs of contraction: in that particular process called stromal reaction that has been seen fostering the progression of neoplastic cells in epithelial tumors. Finally, they have also been found in tissues and organs formed during the embryonic period.

In all these diseases myofibroblasts appear to originate from different cell types. They not only derive from fibroblasts, as was initially thought. In granulation tissue, the fundamental origin is the fibroblast: but in scleroderma, hepatic and glomerular fibrosis, for example, they seem to be generated by pericytes and the smooth muscle cells of the vascular walls.

Recent studies have revealed that a surprisingly high percentage (30-40%) of myofibroblasts of granulation tissue come from the bone marrow cells which, going through the bloodstream, land in the area of damage. \(^{30-33}\) This is an observation of paramount importance as it introduces with validity the hypothesis that the local healing of a disease, whether surgical or internist, is not the result of an oper-

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**Notes**

ation limited to “local” cells. The process instead arises from the contribution of cells situated in a central area far from where they detach, stimulated by specific messages (about which much research is being done). This central area is likely to be the bone marrow, which could play a homeostatic function involving all the tissues of the body. The same basal cell turnover may be under its control (tissue homeostasis). Even organ fibrosis and stromal reactions may occur due to cellular elements from the bone marrow.51

The mechanisms that we have seen integrate themselves into healing processes, and into the resulting deformities, appear to play crucial roles in the pathogenesis of the stenoses that can happen to surgical anastomoses in the alimentary canal, as well as in the pathogenesis of fibroses (whether more or less spread out or more or less restricted) of deep organs, following various diseases, from traumatic to toxic and infectious. In the liver they can resemble cirrhosis. The mass of collagen becomes sclerotic, distorting canal arborization and compromising the regularity of the flow of secretions. The origin of myofibroblasts tracked in these diseases is the subject of research and lively debate. The fibroblasts are not always the precursors. In the liver they seem to be stellate cells.

The presence of stable myofibroblasts in normal alveolar septa has been widely confirmed and believed to be the main source of pulmonary fibrosis. Even in the evolution of cancerous tumors, a contribution from the myofibroblasts of non-local origins is used.49

Piloted healing

Even the modern conception of healing of a wound, from simple injuries to multiple trauma situations, owes much to the study of the burn disease. Not only did it hidden mechanisms, but some clinical observations, for many years were involuntarily kept on the sidelines, have been part of the channel within which the theory of surgical induction was developed in the 90s. Let’s refer to the hypothesis of piloted healing advocated by G. Dogo in the 50s. In a nutshell, it started from the observation of the behavior of a burn wound treated locally with homologous partially devitalized skin which was being preserved in liquid nitrogen. The epithelial component died when frozen, while the dermis retained a certain degree of structural normality (proportional to the damage caused by the freezing) that allowed it to survive longer on the host when used to cover an area in granulation. The prolonged presence on the host seemed to allow for the use of young connective strips among the “semi-degenerate” connective strips of the graft, and suggested that this would lend itself to gradual replacement by the host’s newly formed connective tissue, offering a very useful matrix for the reconstruction of the connective plane of the traumatized surface (creeping substitution possible).

In the competition between healing and regeneration the events seem to undergo a significant moderation which favors the regeneration, leading to less fibrotic repair of the lesion (which therefore has less scarring and is less tight) and with a closer-to-normal structure (piloted healing).

Since then much water has passed under the bridge. Firstly, the mechanisms of creeping substitution have been clarified. Secondly, the role of growth factors has been discovered – the bearers of messages without which every vital process shuts down. Furthermore, the importance of mechanical forces in determining tissue architecture has been understood. And now, the “impetuous onrush of stem cells,” the detection of the ordering capacity of natural and synthetic matrices such as Integra, and developments in tissue engineering are expanding the frontiers of research and therapeutic alternatives far beyond expectations. From the convergence of all these clinical and laboratory experiences, the clinical hypothesis of surgical induction (as a set of measures designed to reproduce anatomic structures which were destroyed or decaying as closely to normal as possible) was bound to come up. Many other disciplines – medical and biological – have made, and continue to make their knowledge available, giving rise to one of the most promising areas of science. We certainly cannot say that all this knowledge originated from the aforementioned observations carried out on burn patients more than half a century ago. Many researchers today are not aware of them since they were published in magazines which had not yet been reviewed.52,53 But to those of us who have been able to closely follow the evolution in time, it is right to recognize the continuity of the studies of yesteryear with today’s multitude of scientific facts, and consider them to be the dawn of the great chapter of “inductive surgery.”

Summary and conclusions

I have discussed some ideas about the contribution of the scientific components of the burn-as-disease to medical science in general – not for the sake of the history itself, but with the conviction that the study of the development of ideas, and thus of their history, is itself a science and can show the right way to move forward into the future. On this note, physician and novelist Dr. Oliver W. Holmes wrote, “When I want to know what is happening today or try to predict what will happen tomorrow, I look to the past.”

The considerations regarding pilot observations may appear biased and saturated with “parochialism”. When supporting the originality of a ‘fact’ or an ‘observation’, one risks clashing with the opinions of others and being contradicted. We must be ready for our ideas to be challenged...
and proved wrong; it may emerge that the truth is something else! We would, however, like to argue that the burn-as-disease, with its insights into pathophysiologicals both clinical and therapeutic, has contributed significantly to the progress of biomedical knowledge. Advances in doctrine and in practice regarding shock (hypovolemic shock), metabolic disorders (hypercatabolism), viable storage and rejection of homologous tissues, scarring, and induction surgery – all have contributed to launching a series of rich conceptual elaborations, from which numerous disciplines have benefited. Indeed, countless scientists in different fields have been able to transfer the knowledge learned to the problems involved in their own research. Each burn specialist must be aware of this extraordinary past and treasure it within their cultural heritage. They must persevere in study and research on the paths which have already been paved (of course not without forging new ones). Finally, they must maintain expertise in the problems had to be faced in the past.

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