Chapter 1

Etiology, Biology and Treatment of Muscular Lesions

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http://dx.doi.org/10.5772/56602

1. Introduction

The detrimental event on a muscular level, founds one of the most recurring traumatic insults in sporting environment. The entity of the lesion can go from simple sprain, often associated with the breakage of small vessels, with appearance of pain and swelling, to complete muscular tear. The consequences for the athlete, which appear linked with the entity of the lesion, are always unpleasant and involve suspension, more or less long, of sporting activity, not to mention suitable therapy.

In this chapter we will try to clear up the different physiological aspects which normally characterize the traumatic event and to describe, even if only summarize, the mechanism of muscular repair.

2. The definition of muscular lesion

Few authors have explicitly defined the term "muscular lesion", even though some have attempted to link the concept of lesion to that of the loss of proper muscular function (Brooks et al., 1995). However, identifying muscular lesion with the simple loss of function isn't altogether correct, indeed muscular function may be nullified by events, such as tiredness or atrophy, which have nothing to do with the detrimental mechanism. For these reasons, even though the concept of functionality loss represents one of the main characteristics of the lesion of the muscle, we believe that the correct definition of muscular lesion cannot overlook the concept of "damage" towards the muscular structure. Therefore, a correct definition in this sense could be the following: " muscular lesion is identifiable by the loss of functionality of the muscle caused by damage, more or less severe, on a level of muscular structure or on a level of anatomical sites assigned to transmit strength", intending with the last explanation

the damage on a level of tendon-muscular passage. This definition clears the concept that in the field of muscular lesion the loss of function cannot be separated from the concept of structural damage.

3. The connection of the contractile apparatus to the extra-cellular matrix

The link of the muscle fibers to the tendon or to the fascia, must have the capacity to resist considerable strength which can go above 1000 kg during maximum type strain (Tidball and Daniel, 1986; Tidball, 1991;). To possess such a great strength, each fiber contains specific molecule chains: integrin and the complex distrofin-glycoprotein (Mayers,2003; Michele and Campbell, 2003). These two complex proteins connect the contractor myofilamentous apparatus to the extracellular matrix(ECM) through the sarcolemma. (Brown, 1996; Giancotti and Rouslathi,1999; Chiquet, 2003; Chargé and Rudnicki, 2004; Ervasti, 2004; Sunada and Campbell,1995; Kääriäinen et al., 2000;). It is necessary to remember briefly that ECM is made up of an intricate network of macromolecules formed by fibrous protein included in an gel of polysaccharides, L'ECM, apart from being particularly present on a skeletal muscle level, it also results in abundance in the connective tissue. The integrins are a family of "adhesion molecules" positioned in the cellular membrane, which cover a fundamental role in many biological processes tied related to the tissue survival, at growth and regeneration. In addition, the integrins actively participate in the cellular communication, for example in the case of signal between cell and cell, of interaction between cell and ECM or in the process of translation of the signal inside and outside the cell itself (Giancotti, 1999, Mayer, 2003; Rouslathi, 1996). In a healthy muscular fiber the majority of integrins are positioned on a level with the junction of tendon muscle (MTJs) (Bao et al., 1993; Kääriäinen et al., 2000a; 2000b; Mayer, 2003) and are organized in a structure specifically named "integrin associated-complex" (figure1). In this complex the sarcomerica terminal ties, through different sub-sarcolemmal molecules, to the sub-unit B1 of the transmembral integrin muscle specific x7B1 (Otey et al., 1990; Song et al., 1994; Yao et al., 1996; Kääriäinen et al., 2000a; Mayer, 2003), which in turn connects the intracellular contractor apparatus with the surrounding ECM by means of the link with the proteins ECM (Burkin and Kaufman, 1999) (Figure1). On the contrary what we can observe for the integrin, whose accumulation is met in proximity of the distal of the muscular fiber the molecules of the complex distrofin-glycoprotein(figure1) are relatively distributed along the entire sarcolemma, even though they result more abundant on a level of the MTJs and the neuro-muscular junction (Sunada and Campbell, 1995; Brown,1996; Hoffman,1996; Cohn and Campbell, 2000; Kääriäinen and et al., 2000a; Michele and Campbell, 2003). The terminal actin ties with the distrofin which in turn ties with three proteic complexes: the distroglicans, the sarcoglicans and the sintrofins (Cohn and Campbell, 200; Ground, 1991; Michele and Campbell, 2003, of these the x-distroglicans tie with the ECM proteins (Michele and Campbell, 2003). The integrins therefore form true " adhesion focal complexes", which form articulated biological systems which show themselves extremely sensitive in comparison with mechanical strengths which stimulate the muscular complex and could, for this reason, perform a key role in the inducing mechanism of hypertrofic phenomena (FLuk et al., 1991). The formation of

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new systems of focal adhesion, could in fact induce a modification of the transcription and translation processes of mRNA, inducing the muscular cell to raise the proteic synthesis and induce the variation the characteristics of the expressed isoforms from the heavy chain of the myosin (Lee et al.., 1991).

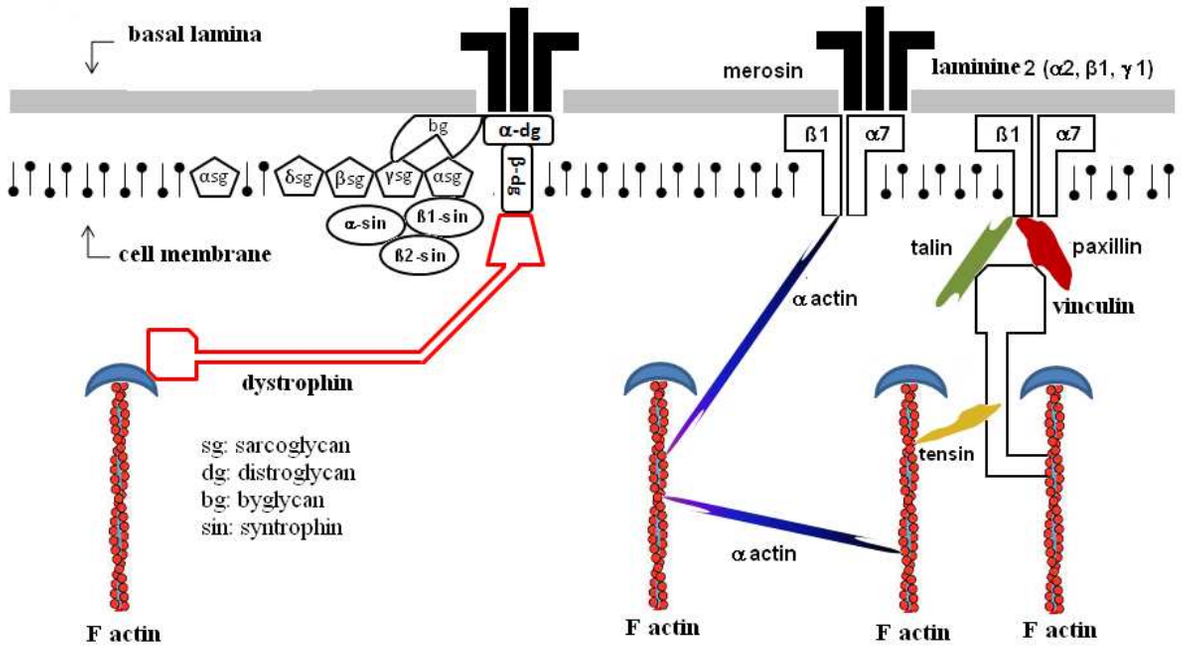

Figure 1. Schematic representation of the adhesion of muscle fiber to extracellular muscular-matrix (ECM). Each fiber contains specific chains of molecules defined integrin and dystrofin, which connect the myofilamentous contractor apparatus to the ECM through the sarcolemma. The main part of the integrin is located in the neuro-muscular junction. The sarcomeric actin ties itself through several molecules, located on a sarcomeral level, to β1 sub-unit of the trasnmembranal muscle specific integrin 7 β1, which is then tied to the ECM protein. The molecules of the dystrofin associated complex, are relatively distributed in a homogenous way along the whole sarcolemma, even though they are particularly abundant in the muscle-.tendon junction and the neuro-muscular junction. The actin ties itself to the dystrofin which is in turn associated with three complex proteins: distroglicans, sarcoglicans and sintrofins.

In the end we have to remember the role of dystrofin as a marker of muscular lesion. Some research conducted on animal models show a conspicuous decrease in coloration of the dystrofin in the muscle immediately after an eccentric contraction (Koh and Eswcobedo, 2004; Lovering and Deyne, 2004). In these studies the loss of dystrofin was associated with the decrease of another membrane protein, the beta-spectrin whose role would seem similar to that of the dystrofin in the stabilization of the membrane. On the other hand the role of dystrofin in maintaining membrane integrity as well as its stability is confirmed by the fact that its missing genetics is at the base of the onset of the Duchenne muscular dystrophy (Hoffman et al., 1987; Zubrycka-Gaarn et al., 1998).

All the same, it is not entirely correct to consider the loss of membrane integrity as a negative event able to compromise muscular homeostasis through the destruction of the barrier which allows the maintenance of an ideal balance between intra and extra cells molecules. In effect a reduced and transitory destruction of the membrane may allow a normal pathway for the

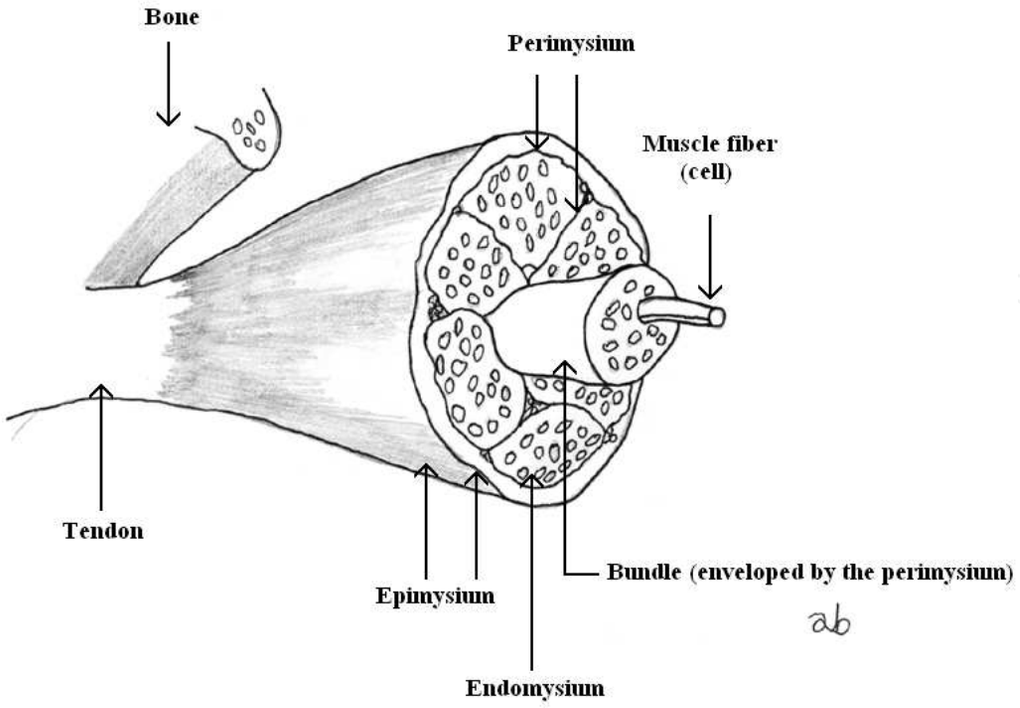

Figure 2. Schematic representation of the skeletal muscle

release and for the assumption of some molecules, above all in tissue exposed to repetitive mechanical stress (McNeil and Khakee, 1992). The muscular tissue in effect shows undeniable capacity in repairing quickly minor entity damage dependent on the membrane structure, limiting in such a way the possible negative consequences. A molecule whose pathway depends on a transitory disturbance of the membrane integrity is the Basic Fibroblast growth factor (bFGF), growth factor strongly concerned in tissue repair processes and in adaptation processes of the muscular tissue regarding strenuous physical exercise. In conclusion a transitory and modest loss of the membrane integrity, can be interpreted also as a physiological answer to the muscular tissue in comparison to intense exercise, answer which is seen in function of the release and transfer of essential growth factors for the repair and functional and biological adaptation of the muscle. If the destruction process of the membrane integrity hesitates towards repair and adaptation, or towards cell death it will depend, obviously, on the entity of the detrimental event in itself and from all the other factors which will contribute to the lesion and repair process.

4. Structural damage and contraction types: An overall vision

The structural damage of muscular fiber may be caused by a singular muscular contraction or by a series of contractions (Armstrong et al., 1991b). In any case the mechanism mainly linked to the possible damage of muscular fiber would be the eccentric contraction (Garret, 1990; Armstrong, 1991b;). The reason of main traumatic incidence on a muscular level, seen during

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General term	Specific muscle term
Muscular cell	Muscular fiber or fiber cell
Cellular membrane	Sarcolemma
Cytoplasm	Sarcoplasma
Mitochondria	Sarcosoma
Endoplasmic reticulum	Sarcoplasmic reticulum

Table 1. Equivalent terminology of the principal muscular terms

an eccentric contraction is above all ascribable to the main production of registered strength, as opposed to how much happens in the during a concentric or isometric contraction (Stauber, 1989; Garret, 1990). In fact during an eccentric contraction, carried out at the speed of 90 s^{-1}, the strength expressed from the muscle appears to be three times more than that produced, at the same speed, during a concentric contraction (Middleton et al., 1994). This higher strength production during an eccentric contraction, is mainly due to the elastic capacity of the tail of the myosin; in fact from the moment that, during an eccentric contraction the production of strength occurs during the detachment of the acto-myosinic bridges, the fact that the tail of the myosin is capable of resisting the detachment thanks to its elastic characteristics, allows a substantial increase in the capacity of strength production during the course of the eccentric phenomena (Middleton et al., 1994). In addition, during an eccentric contraction, the strength appears higher generated by the passive elements of the connective tissue of the muscle undergoing extension (Elftman, 1966). Above all, with reference to this last data we have to underline that also the purely mechanical phenomena of the extension, may play an important role in the onset of traumatic event, seeing as this latter one may prove, either in an active muscle during the lengthening phase, or in a muscular area which, during the extension phase, is totally passive (Garrett et al., 1987). However, the rate of extension in which the muscle risks its structural integrity is quite broad, being between 75 and 225% of its length at rest (Garret, 1990). This data underlines the fact that the muscular injury, due to elongation, does not appear at an relatively constant extension but may depend on many other factors, for example the level of electric activation of the muscle undergoing elongation, or the structural weakness of the latter following previous structural damage. In any case, it is important to notice the fact that some authors sustain the hypothesis that the length at which the muscle comes under extension represents a key factor in the entity of the possible damage, in that a superior initial muscle length corresponds with a superior extension and, consequently, a possible superior structural damage (Talbot and Morgan, 1998). The fact that at a superior length of extension the muscle may produce superior structural damage could depend on the heterogeneously of the length of the various sarcomeres of minor dimension which compose the muscular fiber. In fact, in superior length of extension the sarcomeres of minor dimension undergo a phenomena of "overstretching" whose magnitude would be directly linked to the muscle length which triggers the process of elongation(Morgan,1990).

Regarding the level of muscular activation during the course of extension it is important to know that an active muscle is capable of absorbing much more energy- in terms of tensile energy- in comparison to a passive muscle. So the potential energetic absorption of a muscle is increased drastically when the latter contracts actively (Garret, 1990). This introduces the concept of how a muscle, contracting actively, may put into action a kind of self-blocking strategy following damage due to excessive extension. The capacity of a muscle to resist a lengthening force absorbing energy is represented graphically, in mechanical terms of the underlying area of the stress-strain curve, as shown in figure 3.

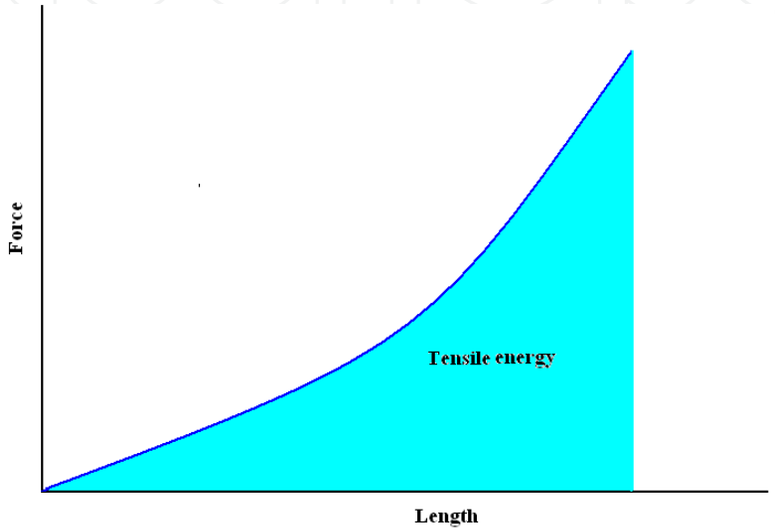

Figure 3. A biological material such as the skeletal muscle, lengthened over a certain length produces a certain quote of tensile energy which, in the graph that shows the rapport strength-length, is represented by the underlying area of the curve.

We may consider that inside the biological muscular structure, there are two structural components able to absorb tensile energy: the passive component and the contractile component. The possibilities of energetic absorption on behalf of the passive component don't depend on the muscular activation, but are essentially attributed to the connective tissue which is found inside the muscular belly but also in the "dumping factor" composed of fiber itself and to the connective associated tissue. The muscle shows however an increase of its capacity to absorb tensile energy thanks to its contractile characteristics, which obviously depend on the level of contraction at the time of extension, as we can see represented in the graph in figure 4.

So there could exist conditions able to diminish the contractile capacity of the muscle and thus reduce its capacity to absorb energy during an extension phase. The muscular fatigue and the structural weakness following a previous lesion, could be two determining factors. It is also important to note that an optimal capacity of absorption of extension strength represents an important protection factor, not only for the muscle itself but also as far as articulation and capsule-ligamentous apparatus is concerned (Radin et al., 1979) In addition, it is interesting to observe that at low levels of elongative tension, the energy absorbed by a muscle is almost totally dependent on the contractile component and, since the normal eccentric muscular

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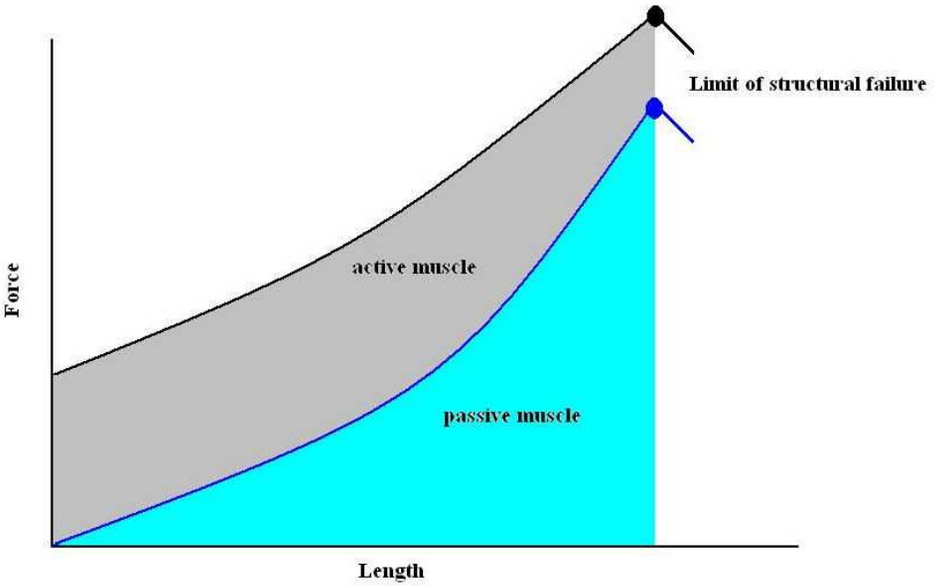

Figure 4. Graphic representation of the force-length relationship in an elongated muscle up to its breakpoint either in passive condition, or in contraction. As is easily recognizable from the graph, the peak of strength of breakage is superior, in the contracted muscle in comparison to the same muscle in relaxed conditions, by a quota equal to only 15%. However, the tensile energy absorbed by the contracted muscle appears superior to that of the same muscle in relaxed conditions. In addition, it is interesting to note that the absorbed energy is superior at low levels of extension (from Garret, 1990, modified).

activity entails quite reduced tensile levels, almost all energy due to tensile stress is absorbed in this case by the contractile component. (Radin et al.,1979)

During the eccentric contraction the muscle undergoes an "overstretching" phenomena which, as such, may determine the onset of lesions on a level of tendon insertion, of the muscle – tendon junction, or on a level of a muscular area rendered more fragile by a deficit of vascularization (Middleton et al., 1994). It is interesting to note how the pluriarticular muscles are the ones mostly exposed to traumatic insult, precisely due to the fact of having to control, through the eccentric contraction, the articular range of one or more articulations (Brewer, 1960). Also the different type of muscular fibers presents a different incidence of harmful event. Fast contraction fibers (FT) are in fact more highly exposed to structural damage in comparison to those of slow contraction(ST), probably due to their superior contractile capacity which translates itself into an increased production of strength and contraction speed, in comparison to fibers type ST (Garret et al., 1984; Friden and Lieber,1992).Furthermore the muscles which present a high percentage of FT, are generally more superficial (Lexell et al., 1983) and are normally interested by two or more articulations, both factors made ready for structural damage (Brewer, 1960; Garret, 1990). To this we can add several studies (Potvin, 1997), which show how in the course of the eccentric phase of movement, the electromyographic activity shows a preferential recruitment of FT fibers.

As well as these hypotheses, it is interesting to note several studies, available in bibliography, which ascribe superior susceptibility to structural damage on behalf of the glycolytic fibers to their particular metabolism (Patel et al., 1998). According to this theory the low oxidative

potential, typical of glycolytic fibers, would predispose the latter to structural damage in the course of repeated eccentric contractions because of the depletion of the highly energetic phosphates. This situation would cause the formation of actomyosinic bridges in "rigor state" particularly exposed, because of their excessive rigidity, to the potentially induced structural damage from the eccentric contraction. However, this hypothesis even though engaging and not void of rationality, wasn't supported by experimental evidence in the course of ulterior studies conducted by the same author, during which it wasn't possible to show, on an animal model, that a superior oxidative potential of the glycolytic fibers, induced by a specific training plan, could represent a protective factor for the possible damage induced by eccentric contraction. Beyond the undoubted differences of metabolic type between the gylcolytic and oxidative fibers, other theories which attempt to discuss a superior predisposition to the traumatic insult of the FT single out the different contents of the latter regarding the level of some cytoskeletal proteins(Koh,2002). These particular cytoskeletal proteins, which are fewer in glycolytic fibers in comparison to those of oxidative fibers, would provide a kind of structural support for sarcomeres and the cellular membrane, contributing in such a way to maintain the integrity of such anatomical structures towards mechanical stress represented by eccentric contraction. Koh himself moreover identified in other particular proteic molecules, named "heat shock proteins" which would head to a family of "stress proteins", once again contained in superior quantity in oxidative fibers rather than glycolytic ones, substances able to carry out a protective role towards the muscular structure still during the "induced injury contraction" represented by eccentric contraction.

Another risk factor is represented by the heterogeneity of the sarcomeral length. The sarcomers of minor length represent in fact, the "weak point of the chain" during the eccentric overstretching phenomena (Morgan,1990). To this end it's important to remember that after a muscular lesion we can note, in an animal model, an increase of the heterogeneity of the sarcomeral length (Patel et al.,), this could, at least in part, explain why, a previously damaged muscle, presents a higher risk of traumatic recurrence. In addition, it is interesting to note how the traumatic event is mainly located on a muscle-tendon junction level, witnessing the fact that in this area, just as in the rest of the final portion of muscle fiber, appears the most mechanical stress (Garrett et al., 1987; Garrett,1990; Lieber etal., 1991). Even though to this end we have to remember that some studies (Huxley and Peachey, 1961) show how muscle fiber, in proximity of the muscle-tendon junction, shows a minor lengthening during an eccentric phase, in comparison to the one in its central area. This data could lead us to the hypothesis that the following damage in an eccentric contraction, on a muscle-tendon level, is not so attributable to the size of elongation as such, but to the application of forces of tangential type on a less vascularized area, and thus structurally more fragile. We need to underline the particular metabolic aspect connected to the eccentric type of contraction. During this type of contraction, since the muscular perfusion is drastically diminished with consequential functional deficit of the aerobic mechanism, the physiological activity is mainly anaerobic type; this determines, either an increase in local temperature, or acidosis, in addition to a marked cellular anoxia. These metabolic events translate themselves into an increased muscular fragility and into a possible cellular necrosis, both on a muscular level as on connective tissue (Middleton et al., 1994).

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5. The calcium overload phase

From close examination of international literature it appears clear that, if on the one hand muscular exercise represents a potential source of traumatic events, on the other hand a correct conditioning of the same muscle and its functionality, may reduce considerably the risk of lesion (Ebbeling and Clarkson 1989; Stauber, 1989; Scwane and Armstrong, 1983; Armstrong, 1984). The majority of the studies agrees on the fact that muscular damage is produced, practically in most cases, through an eccentric contraction, during which the muscle elongates at the same time in which it is activated from a contractile point of view (Armstrong et al., 1983b; McCully and Faulkner, 1985; Lieber and Friden, 1988), in addition the muscular damage would seem linked both to the intensity and the duration of exercise (Tiidus and Inauzzo, 1983; McCully and Falukner, 1986).The traumatic event is generally accompanied by a series of clinical and functional problems which are identifiable in : loss of contractile strength, pain, swelling and /or edema, diminution of the contractual capacity, alteration in the proprioceptive muscular pattern and alteration in the strategy of neuro-muscular activation (Davies and White, 1981; Newman et al., 1983; Riden et al., 1983; Armstrong, 1984; Ogilvie et al., 1985; Ebbeling and Clarkson 1989; Darren et al., 1990). The indirect muscular trauma must be visibly distinguished from DOMS (Delayed Onset Muscle Soreness), in fact, if the two biological descriptions present many common points, the DOMS must be anyway understood as a physiological process which poses itself to all effect as a natural forerunner of a process of muscular adaptation aimed at the better functioning of the muscle towards an external load, represented by the training process (Armstrong,1984; Armstrong 1990). The initial detrimental event, drives rapidly to a loss, located inside the injured muscle fiber of the homeostasis of CA^{++} which is named "Ca^{++} overload phase". The muscular cells possess several specific mechanisms deputed to the regulation of the levels of cytosolic Ca^{++} (Carafoli, 1985; Klug and Tibbis, 1988); at the moment in which these buffering and translocation mechanisms are inhibited by the excessive intracellular level of Ca^{++}, caused by the breakage of the sarcoplasmatic reticulum following the injury, we may assist with the activation of numerous pathways of degradation inside the muscular fiber of the injured area. In such a way it activates, on the injured area, a mechanism of autogenetic degradation which includes the activation of the phosfolipase A_2 (PLA_2) with consequent production of arachidonic acid, prostaglandin, leukotrien, Ca^{++} dependent proteases and lysomial proteases. In addition, the increase of intracellular Ca^{++} levels, apart from provoking a sarcomeral contraction reflex (i.e. not interposed from the SNC), may inhibit, or even suppress, the normal mitochondrial breathing. This series of autogenetic factors inside the damaged fiber comes about before the invasion, inside the injured fiber of the macrophages and continues, anyway, also after the appearance of the latter on the damaged area.

6. The hypotheses of onset of muscular damage

Even if the etiology of the event or specific events able to induce damage on skeletal muscle fiber they aren't fully understood, the hypotheses can be, in any case, divided into two

typologies, the first of physical type and the second of metabolic type, even though in many cases these etiological descriptions overlap not allowing, in fact, an unmistakable distinction.

7. The hypotheses of physical type

The possible mechanisms of physical type capable of inducing initial structural damage to the muscular fiber, may be divided into two categories. The first includes the hypothesis of mechanical nature, whereas the second includes those induced by change of temperature. The fact that the muscular damage recognizes in an eccentric contraction its "*primum movens*", is a widely spread concept amongst many authors (Armstrong, 1984; Ebbeling and Clarkson, 1989; Stauber, 1989, Kano et al., 2008; Schache et al., 2008, Chang et al., 2009), so for this reason the mechanical theory of the fibrillary damage, underlines the substantial difference, in terms of strength production, between the eccentric and concentric and isometric contraction, whereas the theory which identifies the damage as consequence of a "temperature-dependent" mechanism is based on the hypothesis that, during an eccentric contraction, the local temperature of the muscle is higher, factor which would predispose the muscular fiber to structural and /or metabolic changes, potentially harmful.

8. The hypotheses of physical type: The theory of mechanical factors

The mechanical theory is essentially based on the central role which covers the eccentric contraction in a harmful process. The skeletal muscle may be defined as a flexible biological material, or a material able to sustain elongation which can also go over 5% of its at rest length (Popov, 1990). However, the skeletal muscle is, at the same time, a compound biological material of complex type and, for this exact reason, the study of its components of structural weakness, which can determine the mechanical yielding, appears extremely difficult. As previously implied, the structural damage depending of muscular fiber may be the consequence, both of a single muscular contraction and of a cumulative series of contractions (Armstrong et al., 1991). During a contraction the muscular fiber may mechanically give way, at the moment in which the tensile stress, to which its structural components are undergone, overtake the maximum production of strength of the same components and goes beyond the said" maximum theoretical stress value" (MTSV). If the tensile stress to which the fiber is subjected, overtakes the MTSV, the structural components give way; in other words an irreversible lesion is produced in the muscular fiber (Figure 5). In a way such as we can see in the course of a monodirectional elongation, such as that described in a stress-strain curve, the muscular structure may give way irreversibly also at the moment in which it undergoes through a stress cutting (i.e. an oblique strength stress), in accordance with what is stated from the "maximum stress-shear theory" said also "maximum distortion-energy theory" (Popov, 1990), in which the acting forces on muscular fiber are considered in a three-dimensional way.

However, the studies of the mechanisms which may cause structural damage to the muscular fiber, have aimed and still aim, also to the cumulative effect of the mechanical tensions to which

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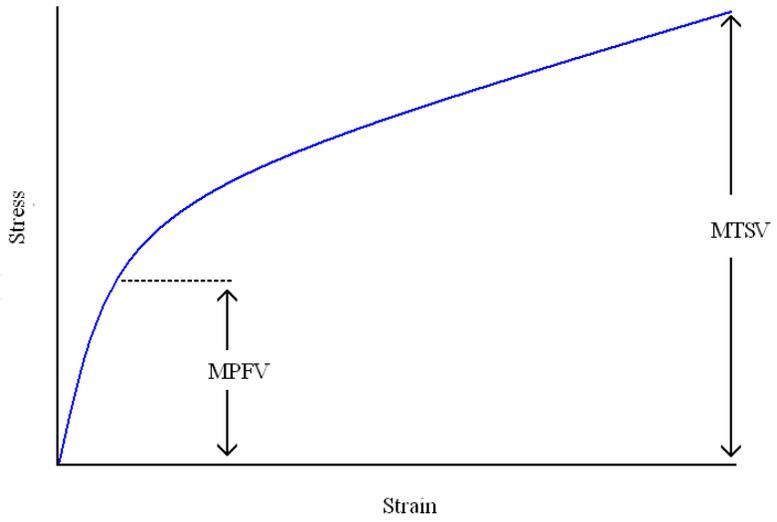

Figure 5. A stress-strain curve, typical of a flexible biological material undergoing tension. The material shows, before the stress which it undergoes surpasses the value of maximum production of strength (VMPF), an elastic type behavior. Once the MPFV is overtaken, the material undergoes a permanent change in form, in other words it undergoes a "plastic deformation". Once the value of maximum force is reached (MTSV) the material gives way irreversibly. From a traumatological point of view we can therefore indentify three different zones in the stress-strain curve of a muscular fiber undergoing tension in the course of an eccentric contraction. The first is included between the beginning of elongation and the value of MPFV, inside which, despite the lengthening stress, the muscular fiber shows elastic behaviour thus not risking structural damage. The second is included between the value of MPFV and the value of MTSV, inside which the fiber surpasses its elastic limits, in which the fiber doesn't show loss of its structural integrity and undergoes a plastic deformation. In this zone the fiber doesn't show loss of its structural integrity. And the last an area which goes beyond the value of MTSV, in which the same fiber gives way. In this last case, *we can observe a muscle tear which severity* - first, second or third degree -is directly linked to the magnitude of the tensile stress to which the fiber undergoes.

the fiber is exposed, focalizing in such a way on the important aspect of the resistance of biological material to the fatigue phenomena. In this particular investigation we study the answer of the biological material at the moment in which the latter is exposed to a high amount of tension and relaxation, up until its breakpoint. For the materials which present a high degree of flexibility, the relationship between the stress to which it is exposed and the number of tension-relaxation cycles which guide to their breakage, is of exponential type (figure 6). To an increase in stress to which the material is exposed, corresponds a drop in the number of cycles which lead to the structural weakening of the same material (Ashby and Jones, 1988). In accordance with what is stated from the theories of the resistance to the fatigue of the biological materials, the energy absorbed by a muscle in the course of a strong elongation, may be eliminated both under form of heat and plastic deformation, intending the latter term a permanent change in the form and in the dimensions of the structural components of the muscular fiber. A plastic deformation, in a biological structure such as the one represented by muscular fiber, may begin with an initial weakening of one or more of its ultrastructural components, which can lead to perpetual tension-relaxation cycles and to a breakage of the structures exposed to tensile stress. In addition, we must underline that the increase in the rate of development of stress tends to reduce the number of cycles which lead to structural

weakening, underlining in this way that the speed of lengthening of muscular fiber may play an important role in the onset of the damage (Armstrong et al., 1991).

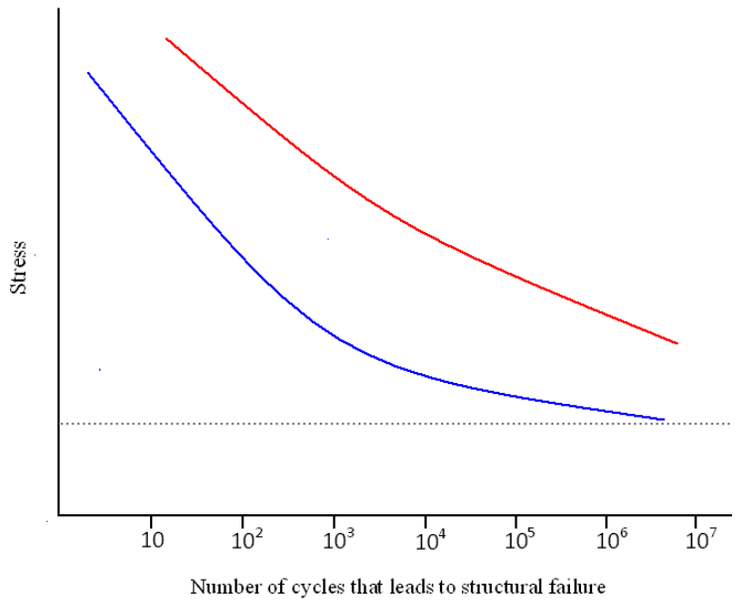

Figure 6. A fatigue curve typical of a flexible biological material. At the moment in which the stress applied during a tension relaxation cycle- also defined from a mechanical point of view as a tension-compression cycle- increases, there is a drop in the number of cycles which lead to the structural weakening. In the graph the dotted horizontal line represents the limit of resistance of the material, (i.e. the stress value under which the considered biological material can support an infinite number of tension-relaxation cycles without incurring structural damage). The red line represents the behavior of a higher resistant material to fatigue in comparison to that of the behavior represented by the blue line (from Armstrong et al.,1991, modified).

The analysis of muscular lesions faced through the given perspective of related literature of the science of materials, appears difficult. The first difficulty which we face is represented by the fact that no data regarding the relationship between the entity of tensile or shear forces and the degree of the lesion doesn't exist. Few studies have in fact investigated, from this point of view, the forces directly expressed inside the muscular structure and even if this type of investigation had been done, the derived values always refer to the registration of forces effected on a tendon structure level. It is important to remember that, in this specific case, the values of such calculated forces represent the sum of values of stress of each single structural component, multiplied by their respective section area (cross-sectional area,CSA). In this way it appears clear that like, from this "global" value, it is difficult, if not impossible, to carry out an analysis of the factors and values of structural weakening for each single component of the considered biological system. A second problem is represented by the fact that individual values of MPSV and of MTSV of the single elements that make up the muscular fiber are, in effect, unknown. A last aspect, problematic in this field, is made up of scarce knowledge of the total capacities of work, in relation to risk lesion, that the skeletal muscle can support during a cycle of eccentric contractions. Above all in this specific field, certain data concerning the loss of percentage of energy absorbed by the muscle and which is dispersed in the form of plastic deformation,. Despite the undoubted conceptual difficulties, from a careful examination of

literature we may glean some important data regarding the capacity of tensile resistance of the muscular fiber towards the eccentric contraction. The first interesting data is represented by the fact that during an eccentric contraction the strength production may surpass a percentage between 50 and 100% the isometric strength maximum value (P0) of the considered muscle (Woledge et al., 1985), in addition, as previously said, during an eccentric contraction, carried out at a speed of 90 degrees, the strength expressed of the muscular area appears to be three times higher than that produced, at the same speed, during a concentric contraction (Middleton et al., 1994). We must remember that this higher production of force during an eccentric contraction, is mainly due to the elastic capacity of the tail of the myosin, which thanks to its elastic characteristics, allows a substantial increase in the capacity of the force production during the elongating phase of the contraction (Middleton et al., 1994). Another interesting aspect is given by the fact that, during an eccentric contraction, to be able to satisfy the principle of an isovolumetric contraction, the CSA of each fiber drops in function of the degree of lengthening to which the fiber is exposed. From a careful analysis of this data, we may presume that the medium value of tensile stress that a muscular fiber actively lengthened during an eccentric contraction of 130% of its length at rest (L0), may be higher from 100 to 160% in comparison to one which appears during an maximum isometric contraction carried out at L0. For this reason regarding the turnover of formation and detachment of the acto-myosinic bridges, it is possible to presume from specific literature some interesting information. The number of acto-myosinic bridges would seem in fact decreasing at the increase of the speed of lengthening of the muscle (McMahon, 1984).This phenomena could involve an increase of the produced force on a level of every single acto-myosinic bridge, predisposing in such a way the contractile proteins of the muscle to the traumatic damage (McMahon,1984). In addition, certain experimental evidence carried out like this would confirm the so far mentioned theories. On preparations of isolated frog sartorious muscle, after only three eccentric contractions, the rate of development of force drops significantly and we may observe a movement of the length-tension curve of the muscle towards superior muscle lengths. However, these changes appear only following a contraction of certain magnitude, and anyway not before force values exceeding 180% (McCully and Faulkner, 1985; 1986). Even though, in current practice, the majority of muscular lesions would seem to occur in the course of particularly fast eccentric contractions, the degree, in terms of severity, of the structural damage of the fiber is mainly linked to the peak of force expressed during an eccentric contraction and not at its intrinsic speed (McCully and Faulkner, 1986). In addition, it is interesting to note that eccentric contractions of magnitude equal to 85% of P0, are able to cause structural damage to the architecture of the muscular fiber, this does not happen during isometric or concentric contractions of the same leve. This particular mechanical behavior, may be explained by the fact that the same peak of force, during an eccentric contraction, is produced at a superior muscular length in comparison to that of one in the course of an isometric or concentric contraction, a factor which would drop the capacity of tensile resistance of the fiber. In fact, the peak of force during an eccentric contraction is reached at a superior length in comparison to that during an isometric or concentric contraction, or on average at 110% versus the 100% of L0 (McCully and Faulkner, 1986; Newham et al., 1988). Since 1939 (Katz,1939) we could state that the harmful process concerning the skeletal muscle was of "length-dependent" type,

meaning by this that the majority of damage to muscular structure happened at the moment in which the eccentric contraction appeared as important muscular lengths and higher than L0; the same data found by Katz was later confirmed by other authors (McCUlly and Faulkner 1985; 1986) So we can affirm that eccentric contractions carried out at higher lengths of L0, cause an excessive tensile stress potentially harmful not only for active elements of the muscular ultrastructure but also for the passive ones, like for example the connective support tissue. In effect this sort of innate structural weakness which the streaked muscle fiber shows during an eccentric contraction, is probably attributable to the fact that, during the amounting of the force peak force in an eccentric contraction The number of active actomyosinic bridges is probably less in comparison to that which we may observe during the peak force fulfillment in an isometric and /or concentric contraction. It is important to underline that in the tension-length curve of the isolated muscular fiber it is proved, by exceeding lengths of L0, a decrease in active tension, which is compensated by a contextual increase of the expressed tension by the passive elements, which in this case contribute to the production of the level of total force, giving at the same time an idea of how much they are stimulated from a tensile point of view during the lengthening of the muscle. For this reason, during the lengthening phase a muscular complex- intended both in active and passive components – is exposed to the harmful event, not only when is electrically active but also in an electrically silent phase. Many authors have underlined the fact that, for a given level of production of force, the generated stress on a level of passive elements of the muscle, is higher during an eccentric contraction in comparison to an isometric or concentric contraction (McCully and Faulkner, 1986; Faulkner et al., 1989). However, it is also true that during a lengthening carried out at the same speed of a lengthening at which an eccentric contraction is carried out- considered in this case like a sort of active lengthening of the muscle- a harmful event does not occur on a structural level (McCully and Faulkner,1986; Faulkner et al., 1989), this means that despite the fact that structural damage is theoretically possible also in the course of lengthening of an electrically silent muscle, it is also true the fact that the tensile load to which the passive elements of the muscle are exposed is not the same during an active or passive lengthening. In effect, there is not much practical or experimental evidence which witness the fact that the passive elements may be damaged during an eccentric contraction. In fact, in these cases the majority of the passive tension, up to higher sarcomeral lengths of 140-150% of L0, is absorbed by the sarcolemma (Casella,1951; Rapoport,1972; Higuchi and Umazume,1986). Due to the inhomogeneities of the sarcomeral length, in the course of an eccentric contraction, the sarcomeres of minor dimension may sustain an excessive lengthening, even if the change in the muscular belly in full is relatively scarce. (Julian and Morgan, 1979; Colomo et al., 1988). In this particular situation, the sarcomeres of minor dimension, due to this undergo a real mechanism of overstretching, they may be harmed or cause a lesion in the nearby sarcomeres. The importance of the sarcomeral integrity, is well illustrated in the diseases associated with of Duchenne muscular dystrophy where we assists in the development in a series of defects on a sarcomeral level. (Bhattacharya et al., 1989) essentially ascribable to a deficiency of dystrofin (Hoffman et al., 1987; Zubrycka-Gaarn, 1988). To this end, some authors (Karpati and Carpenter, 1989) have underlined, for a long time, the fundamental importance of dystrofin for the mechanical stability of plasma-lemma, above all what concerns the maintenance of a correct alignment between basal lamina

and the same plasmalemma. Some experiments carried out on frog semitendinosus muscle, show how an important loss of energy at the same time as an increase of the sarcomeral length appears, postulating in such a way that the so dispersed energetic quota may be dispersed under heat form, or in plastic deformation of the sarcolemma, of the sarcoplasmatic reticulum, of the basal lamina or of the cytoskeleton (Tidball and Daniel,1986). Globally from the same data, we may deduct that about 77% of the total energetic dissipation, which happens in the course of a stretching-shortening cycle, is dissipated on a basal membrane level. This same data was confirmed by other experimental studies (Stauber, 1989), which showed histochemistry and immune histochemistry evidence of damage on a basal lamina and endomysium level in a muscle undergoing a eccentric contraction. Also, the theory of the inhomogeneity of the sarcomeral length- and consequently of the phenomena of overstretching to which they were exposed, during an eccentric contraction, the sarcomeres of minor structural length- was later confirmed also by following studies (Morgan, 1990). Morgan also proposed a sequence of well defined events in this sense:

a. The eccentric contraction carries some sarcomeres whose length is minor in comparison to the average sarcomeral length- to be over-tensioned.

b. The over-tensioned sarcomeres are not able to relax conveniently during a contraction-time/relaxation-time cycle.

c. Above all, in the course of a cycle of particularly fast eccentric contractions the over-tensioned sarcomeres, and for this reason incapable of reaching sufficient relaxation during a succession of contractions, transfer the tensile stress onto the nearby myofibrils.

d. Following the transfer of an excessive tensile stress, the sarcolemma and the sarcoplasmatic reticulum of the nearby fibers to the over-tensioned sarcomeres it structurally gives in.

This theory is, at least partially, supported by data supplied by McCully and Faulkner (1986) who showed how there was no evidence of structural damage when the lengthening speed was reduced under a certain limit. In any case, the data supplied from the experimental studies of McCully and Faulkner, give evidence that the structural components of the muscular fiber may meet up with a fatigue phenomena connected to the repetition of an eccentric contraction. Of particular interest is the strong link, shown by the same authors, between the increase in number of the eccentric contractions, the decrease of the peak of maximum eccentric force of the muscle and the increase of the areas of structural weakness inside the same muscle. This data suggests how the degree of lesion may be proportional to the complex amount of eccentric work carried out by muscular fibers. From the data of the work of McCully and Faulkner, we could draw two important conclusions, which have considerable relapses on a practical/rehabilitative plane and that is:

i. The muscle would have a maximum limit of eccentric contractions beyond which a progressive phenomena of structural weakness would start which could lead to structural damage.

ii. From the time that a progressive increase of the number of eccentric contractions, it would lead to a contextual progressive decrease of the peak of maximum eccentric force, due to the fatigue phenomena, expressed by the muscle, there would exist a limit of the value of eccentric force, below which the muscle would be exposed to the risks of structural damage. According to McCully and Faulkner, such a limit would be between 60 and 80% of the maximum value of eccentric force. In other words when the decrease of the production of eccentric force drops below 20-40% the muscle runs the risk of injury.

From a practical but above all rehabilitative /preventive point of view, this data underlines the importance of:

i. Increasing the muscle capacity in the field of specific stamina regarding the eccentric contraction, in such a way to increase the quantity of eccentric work supported by the same muscle, moving the curve of structural weakness of the relation "stress-number of cycles leading to structural weakness", up and to the right,

ii. Increasing the maximum value of eccentric force, limiting the decrease of the latter in conjunction with the increase of the number of cycles. To this end it is important to remember how the value of stamina- in this case of stamina in eccentric regime- depends on the values of maximum force- and so in this specific case of maximum eccentric force.

9. The hypotheses of physical nature: The role of the increase in temperature in muscular damage

Numerous studies (Nielsen 1969; Nadel et al.,1972; Pahud et al., 1980) witness the fact of how the intramuscular temperature is higher during the negative work (i. e. eccentric contraction) in comparison to that seen in the course of positive work (i.e. concentric contraction) when the data is compared to a metabolic equivalent or to a ratio of heat production (for further in-depth analysis please see the specific box). In equivalent experimental conditions the eccentric contraction, in comparison to the concentric one, produces an increase in heat superior of about 1.2 degrees Celsius (Nadel et al., 1972), sufficient increase to determine a decrease of the viscosity of the sarcolemma equal to about 7% (Nagamoto et al., 1984). Such decrease in viscosity, although modest, would be able to activate the phospholipase A_2, triggering in such a way an increase in the ratio of degradation of the cellular membrane (Chang et al., 1987). Other studies, carried out on muscle in vitro, would highlight as an increase of the temperature from 25 to 35 ° Celsius obtained by placing the muscle under a series of eccentric contractions, increases the risk of structural damage by a good 50% (Zerba et al., 1990) However, we must adopt care in interpreting the role of the increase of the muscle temperature in the field of its structural damage. Such care is obligatory above all considering the fact that, in the mentioned studies, the difference between the peak of temperature obtained during negative and positive work is essentially modest; secondly the absolute metabolic ratio would not seem, in this specific field, the most discriminating parameter. In addition to this, we must consider that

the Fenn effect would theoretically foresee a ratio of minor heat during an eccentric contraction, in comparison to the theoretically predictable one in the course of an isometric and concentric contraction. In effect, the theoretic forecast carried out based on the Fenn effect, which would foresee a minor heat production during an eccentric contraction, would be confirmed also in some experimental data (Abbot and Aubert, 1951). All these observations could lead us to consider the highest production of heat observed in the course of negative work, not so much as an increase in the ratio of heat production on behalf of the muscle itself in similar conditions, but as the consequence of the drop of the ratio or heat removal by the muscle, which is registered during an eccentric contraction (for further information please refer to the specific box.)

9.1. Eccentric contraction and heat dispersion

The production of metabolic heat and its disposal, may be modeled through a central "heat producer" nucleus, made up of skeletal muscles, bowels, internal organs and the central nervous system, a "means of transport", made up of the circulatory system and of a "cooling surface", made of skin. During an eccentric contraction we can see a transient and intermittent mechanism of vasoconstriction which strongly limits the capacity of transporting heat, produced by the muscular contraction, on the part of the circulatory system. For this reason the highest production of heat during negative work, in comparison to the production of heat during positive work, it is essentially attributable to the reduced ratio of degradation of heat which occurs during negative work, caused by the aforementioned vasoconstriction mechanism.

10. The metabolic hypotheses: The role of insufficient mitochondrial respiration

In the course of physical exercise the mitochondrial respiration appears high together with the synthesis and hydrolysis of the ATP. This situation is well balanced from a physiological point of view in the course of moderate exercise in which, the muscular fibers in activity, manage to maintain the concentration of ATP near to the base values (Krisanda et al.,1988). However, in the course of intense and prolonged exercise, a certain reduction in the concentration of energetic phosphates constantly occurs (Krisanda et al.,1988) and the possibility that this event occurs inside some specific compartments of the fiber represents a concrete and reasoned hypothesis which could explain the initial events of the mechanism of muscular lesion. For example, in the case in which a drop in ATP levels occurs near the Ca^{++} - ATPase on a level of the sarcoplasmatic reticulum or of the sarcolemma, the removal of Ca^{++} from the cytoplasm could result compromised, causing in such a way an increase in cytosolic Ca^{++}. To this end there exists important experimental evidence which show that, to maintain an optimal state of cellular function, it is of vital importance to maintain an optimal functionality of the Ca^{++} pump (Duncan, 1987). Also in this field, some studies have shown how a drop in the cellular energetic provision may lead to a release of Ca^{++} from the sarcoplasmatic reticulum (Duchen

et al., 1990). Some physiological evidence would show that the deficit of mytochondrial respiration inside the muscular fiber, cannot be considered the same way as an initial event in the onset of muscular damage; these affirmations are based on the fact that, a given level of production of force and /or mechanical power by the muscle, generated through an eccentric contraction, would result less costly than it is for the same level of production of force and /or generated power through a concentric or isometric contraction (Infante et al., 1964; Curtin and Davies, 1970; Bonde- Peterson et al., 1972) Despite this, it is the eccentric contraction the type of contractile muscular behavior which show higher harmful potential towards the integrity of the muscular structure (Asmussen, 1956; Armstrong et al., 1983; Newham et al., 1983; Armstrong, 1984; Ebbeling and Clarkson, 1989; Stauber, 1989). This lack of linking between metabolic cost and harmful event in the course of an eccentric contraction, would indicate, according to some authors, that the etiology of the muscular lesion would not lead to an insufficient production of ATP. Some authors have shown how there are no changes in levels of ATP, CP or in the pH after an injury, even though 24 hours after intense exercise we may register a significant increase in inorganic phosphate levels (Aldridge et al., 1986) At the same time, it is reasonable to expect that during a series of concentric contractions the muscular pH is lower than what it would be during an eccentric contraction. This could represent another indirect test of the fact that the lowering of the pH cannot, in itself, make up the initial factor of muscular damage. In this sense there exist experiments which show how, on isolated muscle, we may induct muscular damage also in the presence of neutral pH (between 7.3 and 7.6) with an average of 3mmol of lactate per liter (Duncan, 1987) Despite this it is of extreme importance to underline that these studies, and the consequential hypotheses, even though logical and rational, do not make up the indisputable test of the fact that the depletion of ATP or the lowering of the pH, are not implied in the process which carries to the muscular damage, but how rather they show that the muscular damage can come about also in absence of these assumptions of metabolic order (Armstrong et al., 1991). Particular attention must be placed on the fact that these specific situation of " metabolic unevenness", may be focal inside the fiber, reason for which in a well defined area of muscular fiber we may observe essential depletions of energetic phosphates and /or accumulation of lactate, which, on the contrary, are not observed in the rest of the muscular belly. So, even though definite demonstrations are missing of the fact that muscular damage recognizes its etiological cause in an insufficient mytochondrial respiration ratio, in bibliography there are not missing studies which speculate how the muscular damage, above all against the pure glycolytic fibers, at least on an animal model, is amenable to the contextual eccentric mechanism to a metabolic situation predisposing the damage itself (Liebere and Friden, 1988). In effect, a higher rational hypothesis in this sense is that which sees the intermittent anoxia, of which the muscle suffers during an intense series of eccentric contractions, as the cause of the drop in muscle pH to which follows a potential structural fragility situation both of the contractile tissue and of the connective tissue inside the muscle itself (Armstrong et al., 1991). So generally, a marginal fatigue may make up, at least from a theoretical point of view, a predisposing situation to muscular damage, even if a precise estimate of the role of fatigue in the harmful mechanism at the expense of the skeletal muscle, is objectively difficult.

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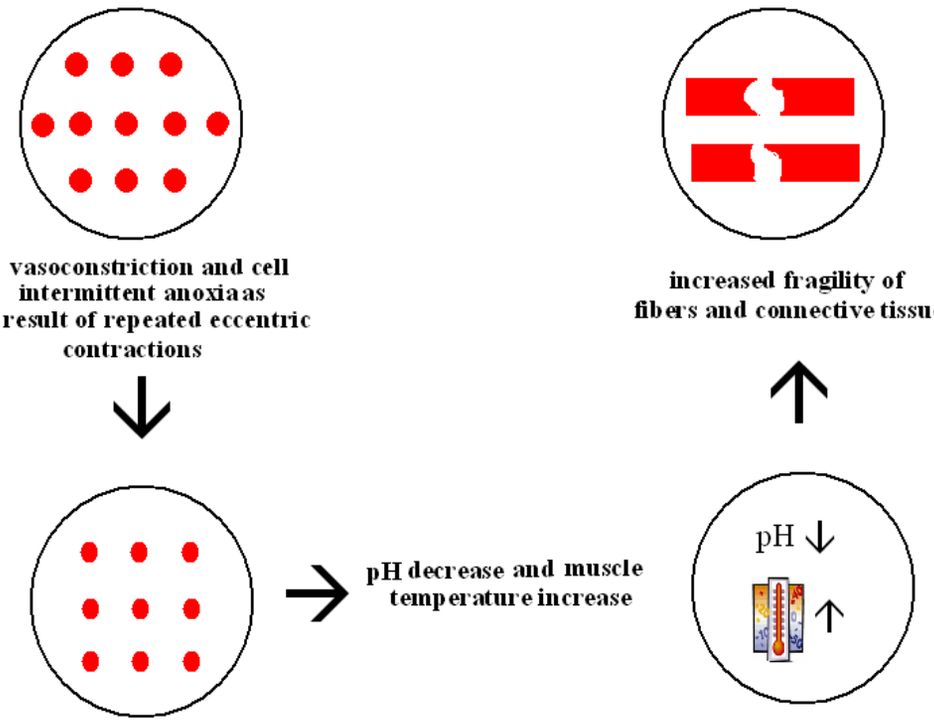

Figure 7. In a muscle exposed to a series of intense eccentric contractions, a capillary vasoconstriction may happen which can, in itself, be the cause of an intermittent and transitory anoxia inside the muscle belly itself. The drop if the efficiency of the mechanism of mitochondrial respiration, would cause a drop in the production of ATP provided by the aerobic mechanism, which would induce an even higher involvement in the energetic production of the anaerobic lactate mechanism. This, together with the loss of efficiency of the heat regulator mechanisms due to the phenomena of vasoconstriction, would cause a drop in the pH and an increase of the muscular temperature, factors which would lead to an increase in the fragility both of the myofibrils and the of the sustaining connective tissue predisposing, in such a way, the muscle to harmful event (Armstrong et al., 1991).

11. The production of free radicals

Another consequence of the increase in metabolism during exercise is represented by the high production of free radicals (Packer, 1986; Jenkins, 1988; Matsunaga et al., 2003; Kon et al., 2008). Even though in many situations the increased production of free radicals is controlled by a wide variety of enzymes and of anti-oxidant molecules (Xu et al., 1997; Kon et al.,2008), in other circumstances this protective mechanism may result inefficient (Demopoulos, 1973b; Jenkins, 1988; Horakova et al., 2005). An uncontrollable production of free radicals may cause damage on a cellular level through an oxidation mechanism of phospholipids (Demopoulos, 1973; Blake et al., 1987) of DNA, (Cochrane et al., 1988), of carbohydrates (Blake et al., 1987) and of proteins (Tappel, 1973; Wolffe et al., 1986). The lipoperoxidation of the lipidic membrane may alter the normal permeability of the barrier of the sarcolemma (Quintanihla et al., 9182), allowing in such a way an abnormal molecular diffusion, in particular of Ca^{++} and of intra-muscular enzymes (Braughler, 1988); the inactivity of this enzyme can in fact perturb the homeostasis of the Ca^{++} inside the muscular fiber and cause, consequentially, the activity of a

series of cellular degradation processes. However, research which supports in an evident way the role of free radicals in the etiology of muscular lesion, is quite limited, above all if linked to an eccentric contraction as principal mechanical cause. One of the most convincing studies in this field is represented by that of Zerba in 1990 (Zerba et al., 1990), in which the authors showed how, in a murine model, an intraperitoneal injection of superoxide-dismutase limits, after the imposition of a series of eccentric contractions in situ, the drop in the value of P0 of the considered muscle. The treatment based on superoxide-dismutase was able to reduce the drop in the value of P0 for a period of three days following the eccentric exercise. Other experiments, carried out on animal models have further corroborated the hypothesis formulated by Zerba (Strosova et al., 2005; Kon et al., 2007), so for this it appears reasonable to extend this theoretical model also in a human field (Castilho et al., 1996; Close et al., 2005; Clanton, 2007; Kerkweg et al., 2007; Voss et al., 2008). There is not missing, however, in literature studies which deny the thesis that the administration of anti-oxidant agents may reduce muscular damage connected with high intensity exercise (Warren et al., 1990; Childs et al., 2001; Sacheck and Blumberg, 2001; Kerkweg et al., 2007). It is also important to remember some interesting experiences (Brooks et al., 2008) which underline the fact that the production of free radicals, on behalf of the skeletal muscle, and consequently their control and their regulation, are in function of precise physiological stimuli and how these parameters play a very important role in the field of physiological adaptation of the muscle during the contraction mechanism. These adaptations would include an optimization of the contraction mechanism, and in addition they would represent the beginning of adaptation processes and changes of gene expression regarding stress induced by the muscular contraction. Evidently these beneficial effects of the free radicals in the field of muscular contraction, contrast with contrary scientific evidence, which see the beginning and /or the cause of free radicals of a pathway of degenerative type which would appear fundamental, not only in the field of possible structural damage regarding the skeletal muscle, but also, more in general, in its aging process. This only apparent contradiction, underlines the necessity of deeper understanding in the role covered by the free radicals in the field of both physical exercise and the sarcopenia. Anyway, despite the relative lack of convincing and undisputable scientific evidence concerning the role of free radicals in the field of initial mechanisms, and /or predisposition of muscular lesion, it is without doubt legitimate to ask ourselves this question: is it reasonable to be able to support an increase in production of free radicals during an eccentric exercise? To answer this interesting and legitimate query, it is useful to remember that some studies (Brand and Lehninger, 1975) show how during an ischemic phenomena, in a model of ischemic /reperfusion damage, we can see in the cardiac muscle a destruction of the normal tight association between the elements of the chain of transport of the electrons. This would provide a particularly evident production of free radicals during the reperfusion phase, phase in which we may find high concentrations of O_2 of the tissue(Hess et al., 1982; Arkhipenko et al., 1983; Faust et al., 1988; Fisher, 1988). It is possible to speculate that the high and specific muscular tensions which happen during of eccentric contraction, may alter the normal cytoskeletal structure, of which whose functions are to stabilize the position of the mitochondria (BIgland-Richie and Woods, 1976). The destruction of the cytoskeleton l could, in its turn, cause a disruption of the spatial configuration of the elements which compose the electron transport chain (Demopoulos, 1973a). This

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structural disruption of the electron transport chain could lead to an excessive production of free radicals and so to a dramatic increase of the lipoperoxidation phenomena. So, in general, every disruption of the electron transport chain, may lead to an increase in the production of free radicals and potentially represent an initial mechanism in the field of the phenomena which we can name as "Exercise-induced muscle fiber injury".

12. The loss of Ca^{++} homeostasis

If the initial events of harmful mechanism are of mechanical and metabolic nature, the immediately successive phases leading to the same harmful event, are characterized by an elevation of the levels of intracellular Ca^{++} in the injured area (Statham et al., 1976; Publicover et al., 1978; Kameyana and Etlinger, 1979; Baracos et al., 1984; Carpenter, 1989; Boobis et al., 1990). It is interesting to note how also in patients affected by muscular dystrophy and other muscular pathologies, we may find an increase in the intracellular levels of Ca^{++} (Jackson et al., 1985 ; Turner et al., 1988). The importance of maintaining the concentration of free cytosolic Ca^{++}, is indirectly underlined by the number of the Ca^{++} transport mechanisms from the cytosolic compartment which the cell possesses (Gillis, 1985; Klug and Tibbits, 1988). There exists, in fact, at least seven membrane transport systems of Ca^{++}. In the actual state of knowledge in the specific field, it would seem that there exists, until today, direct evidence of the fact that the elevation of the intracellular levels of Ca^{++} is involved in the mechanism of "exercise-induced muscle fiber injury" (Hall-Craggs, 1980; Steer and Mastaglia 1986; Childs et al., 2001), even if studies exist which show how in the condition of DOMS, they are present inside the muscle of high contextual levels of Ca++ to a same increased level of mitochondrial Ca^{++} (Duan et al., 1990a). The hypothesis that would justify an increase of intracellular levels, are essentially based on to the destruction of the sarcolemma found during the harmful event. The sarcolemma in fact represents a suitable barrier for the maintenance of concentration and of the electric gradient between the intra and extra cellular spaces; its destruction so permits the Ca^{++} to invade the intracellular space. The concentration of free extracellular Ca^{++} oscillates between 2 and 3 $mmol.1^{-1}$ whereas that of cytosolic Ca^{++}, in the muscle fiber at rest, is about 0.1 umol1-^{1}. So it evidently appears how, at the expense of Ca^{++}, there exists and important gradient between the intra and extra cellular space and that how each loss of normal permeability of the barrier, represented by the sarcolemma, may cause an important influx of Ca^{++} in the intracellular space. In experiments carried out on muscular fibers treated with saponin and incubated in Ca^{++} solution in concentration between 0.5 and umol- 1^{-1}, we may observe a destruction of the myofibrils and a hyper-contraction of the sarcomeres. (Duncan, 1987). From the moment in which such concentrates enter in the same physiological range seen during an "*in vivo*" muscular contraction, this experimental data could induce us to believe that also during normal contractile activity the level of free cytosolic Ca^{++} could be high enough to start the degradation of the muscular ultrastructure. However, this event does not happen above all because the increase of the level of cytosolic Ca^{++} in the course of an *in vivo* muscular contraction is of transient type; In other words at the moment in which the Ca^{++} is released from the sarcoplasmatic reticulum in the course of the contraction itself, its level is readily

limited by the regulating proteins, in such a way that its level seems high only for a short amount of time, and too scarce to allow the activation of proteolytic enzymes (Robertson et al., 1981) ; in addition the proteolytic enzymes inside the fiber are in compartments and for this reason are not influenced by the increase of the level of Ca^{++} which happens during the stimulus- contraction cycle. So, the damage to the muscular membrane or to the sarcoplasmatic reticulum, may be caused by an increase of the concentrate Ca^{++} only in those compartments, inside the muscular fiber, where Ca^{++} is allowed to arrive in contact with the areas of degrading enzymes. (Duncan, 1987). So essentially, it would not be the absolute level of Ca^{++} which can represent an important starting factor of the process of muscular damage, rather than the temporary length of the magnitude of active movement of Ca^{++} through the muscular fiber (Duncan, 1987). In some experiments which simulated an injury, similar to that which can happen following an eccentric contraction obtained by using micro injections on the sarcolemma, we observed the area of necrosis corresponding to the place of insertion, was literally "surrounded" by a sort of barrier, made up of hyper-contracted filaments, in which we could find an increase in the concentration of Ca^{++} (Armstrong et al.,1983b; Ogilvie et al., 1988). A similar mechanism may probably be observed also following an "exercise-induced muscle fiber injury" (Armstrong et al., 1983b; Kuipers et al., 1983; Ogilvie et al., 1988). Many muscular disease show an increase of the levels of intracellular Ca^{++}, caused by the disturbance of the normal barrier permeability of the sarcolemma regarding the Ca^{++} itself. For example in muscles affected by the of Duchenne muscular dystrophy, the proteic degradation is directly linked to the increase in intracellular levels of Ca^{++} (Turner et al., 1988). Another example in which we can observe a high concentration of Ca^{++} is represented by the malignant hyperthermia, in which a specific agent causes a prolonged increase of the concentration of intracellular Ca^{++} which, in its turn, provokes a massive and uncontrollable muscular contraction, whose consequence is an increase in body temperature which can reach 46° C (Cheah and Cheah, 1985). A second mechanism responsible for the elevation of free cytosolic levels of Ca^{++} is represented by the malfunction of the sarcoplasmatic reticulum. Apart from the fact that this happens, following an eccentric contraction which has caused muscular damage, represented by a flux of Ca^{++} from the extracellular space (Duan et al, 1990b) it would still seem certain that the malfunction on behalf of the sarcoplasmatic reticulum in re-absorbing Ca^{++}, may contribute to the increase of its cytosolic concentration. In effect the sarcoplasmatic reticulum reduces its re-absorbing capacities of Ca++ reduced in the course of exercise, both in the case that the intensity of the latter is moderate or maximal (Byrd et al., 1999). However, there is no certain data which can enlighten us in regards to the different possible effects of eccentric, concentric or isometric exercise on the functionality of the sarcoplasmatic reticulum. In any case, it is plausible to put forward the hypothesis that the inhomogeneity of the sarcomeral length can negatively influence on the adjacent segments of the sarcoplasmatic reticulum itself (Armstrong et al., 1991). Some experiments on isolated muscle would go into effect in this sense. When an isolated muscle is incubated with caffeine- a substance which stimulates the Ca^{++} inducing its release on behalf of the sarcoplasmatic reticulum - it is possible to observe a deterioration of the myofibril structure (Duncan,1987); in other respects also the incubation of isolated muscle in ruthenium red - substance which inhibits the Ca^{++}-ATPase - is able to induce significant damage of the myofibril (Duncan et al., 1980). This experimental data witnesses the

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fact that a loss in the homeostasis of Ca^{++}, as in the case of muscular injury, could be, at least in part, due to a malfunction and/or and drop in the efficiency or normal re-absorbing machanisms of Ca^{++} on behalf of the sarcoplasmatic reticulum. Some authors, to this end, emphasize the fact that the mechanisms which cause the destruction of the membrane, are mainly responsible for the increase in levels of intracellular Ca^{++} inside the injured fibers (Armstrong et al. 1991), even if we have to admit the existence of other numerous factors able to perturb the homeostasis of the latter. For example some studies (Snowdowne and Lee, 1980; Lopez et al., 1985) would evidence the existence, inside the skeletal muscle, of "stretch-sensitive calcium channels" ; so - from the moment the muscle during an eccentric contraction is mechanically elongated at the same time in which it is electrically active- the hypothesis appears more than plausible that these specific channels are involved in mechanisms which induce, during the eccentric contraction itself, the increase in intracellular Ca^{++} levels. Another mechanism which could be implied in the increase of intracellular Ca^{++} would be the pathway of Na^{+}: Ca^{++}, through which the mechanism of uptake and the release of Ca^{++} on cellular level is completed, (Allen et.al., 1989), even if in truth there isn't any unequivocal evidence of its involvement in the field of Ca^{++} overload mechanism observable in the injured skeletal muscle. It has also been shown how the inhibition of the acetylcholinesterase on a level of neuro-muscular junctions, causes and influx of Ca^{++} inside the muscular area, contextual to contraction of the fibers and local necrosis of the latter (Leonard and Salpeter, 1979). Also other similar experiments, which have induced an increase in the release of Ca^{++} on behalf of the sarcoplasmatic reticulum have permitted to observe an increase in the contraction of the fibers, together with a rapid process of destruction of the myofibril structure- which happen in less than 30 minutes- in addition to a drop of the intramuscular enzymes (Duncan, 1987). This data underlines the importance which the role of an increase in intracellular Ca^{++} levels could have in the field of construction of the theoretical model of "exercise-induced muscle fiber injury". One of the consequences of the elevation of the level of intracellular Ca^{++} is represented by the phenomena called "blebbing" which consists in the formation of cytoplasmic vesicular enlargements on the cellular surface. We retain that these alterations are to be put in relation with a possible disturbance of the relationship which runs between the cytoskeletal proteins (in particular actin and tubulin) and the cell of the membrane (Orrenius et al., 1989). The "blebbing " phenomena is furthermore observable also outside the model represented by the skeletal muscle, like for example in the cells of the myocardium in the field of the model of "ischemia-reperfusion" (Ganote and Humphrey, 1985; Ariel et al., 2008). In the light of what we have already said, in the field of the theoretical model of "exercise-induced muscle fiber injury" we may think that, during exercise itself, an initial damage occurs, of probable mechanical nature, at the expense of the designated components for the maintenance of a correct permeability of the barrier regarding extracellular Ca^{++}. This alteration would allow a massive diffusion, through the damaged membrane site, of Ca^{++}, giving origin, in such a way, to the said phenomena of "Ca^{++} overload", whose consequence is represented by the annihilation of the tampon systems of the muscular fiber (like for example the Ca^{++} binding proteins, the functionality of the sarcoplasmatic reticulum and the mitochondria). Once the level of cytosolic Ca^{++} has reached a critic level, which remains for a sufficiently long level of time- and

above all if the latter stays high inside the specific compartments of the fiber - different degradation mechanisms start inside the injured muscle fiber which are represented by:

- The mechanism of the myofibrillar reflex contraction
- The phenomena of mitochondrial Ca^{++} overload
- The mechanism of activation of the dependent Ca++ protease
- The lysosomal protease
- The pathway of the A^2 phospholipase

13. The mechanism of the reflex myofibrillar contraction

The loss of the homeostasis of the Ca^{++} involves an uncontrollable contractionreflex (or not through the SNC) by the sarcomeres inside the injured area (Ogilvie et al., 1988). We need however to specify that the myofibrillar contraction reflex phenomena, does not have to be necessarily understood as a degradation phenomena in the strict meaning, like for example the enzymatic pathway could be. Even if some authors have put forward the hypothesis that this zone of concentration may make up a sort of barrier apt to block the degradation processes preventing the latter to extend to the sarcomeres adjacent to the injured zone (Carpenter and Karpati, 1989), we need to consider that this uncontrolled state of contraction of the sarcomeres may have serious consequences in the field of aggravation of structural damage. The first negative effect is represented by the local depletion of ATP following the endurance of the contraction itself, which would give origin to a vicious circle, and so, capable of auto sustainment, identifiable in "depletion of ATP- increase in levels of Ca^{++}" and vice versa (Goodman, 1987). The second negative outcome of the mechanism of myofibrillar contraction reflex is made up of the fact that such a phenomena produces mechanical forces, inside the fibers able to damage further both the membrane and the same contractile components, contributing in such a way to further deterioration of the clinical situation (Armstrong et al., 1991).

14. The phenomena of mitochondrial Ca^{++} overload

The mitochondria inside the muscular fiber have, among their tasks, also that which to react to "buffer", or to tampon mechanism, regarding the increase of the concentration of cytosolic Ca^{++}. However the hypothesis is generally creditable that the uptake of Ca^{++} on a mitochondrial level is quite modest, and in any case insufficient to be able to consider as fundamental, or at least important, the role taken on the mitochondria itself in the field of the mechanism of relaxation of the muscular fiber. Even though we need to remember that the mitochondria, in particular pathologic situations, are capable of accumulating a large quantity of ions (Gillis, 1985). Between all the types of fibers, the oxidative ones show marked capacity of mitochondrial buffering regarding the Ca^{++} which can exceed the registered ones by 2-3 times on a

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glycolitic fiber level (Sembrowich and Quintinskie, 1985). An excess in uptake of Ca^{++} on behalf of the mitochondria is accompanied by a contemporary uptake in phosphates causing, in such a way, a precipitation of calcium phosphate which can deposit itself in the intra-mitochondrial spaces (Gillis,1985). So, on the one hand, an increase in the level of mitochondrial Ca^{++}, which stays in a nano-molar range, appears useful in stimulating the mitochondrial respiration, whereas on the other hand an accumulation of Ca^{++}, in a micro-molar range, causes a depression of the respiratory functions on a level with the mitochondria itself (Wrogemann and Pena, 1976; Hansford, 1985; McMillin and Madden, 1989).

15. The mechanism of the dependent Ca^{++} protease

The Ca^{++} dependent protease is of two types: type 1 and type 2: this division is based on the level of Ca^{++} necessary for their activation. The type 1 isoform is activated in presence of micro-molar levels of Ca^{++}, whereas the type 2 form needs quantities in milli- molars for its activation (Murachi et al., 1981). Unlike not for the lysosomal protease, this enzyme has it optimal pH in the field of neutrality. Its activation is associated with the degradation of particular structures inside the myocell and in particular in the degradation of the Z band (Bush et al., 1972; Ishiura et al., 1980), of the myofilaments (Daytona et al., 1976; 1979; Cullen and Fulthorpe, 1982) and of the A band (Friden et al., 1981; Newham et al., 1983; Ogilvie et al., 1988). All these alterations are observable in an injured muscle following eccentric exercise. Also the proteins of the cytoskeleton would represent a preferential underlayer for the action of the Ca^{++} dependent protease (Pontremoli and Melloni, 1986) To this end, there has been a hypothesis that the proteolysis of the vinculin (a protein of the cytoskeleton which anchors the cellular membrane to the cytoskeleton) on behalf of the Ca^{++} dependent protease, causes a fragility of the sarco-lemma of the myocardium cells in the course of the ischemic process (Steenbergen et al., 1987a).

16. The lysosomal protease

Since the myofibrillar protein may be degraded by the proteolytic enzymes contained in the lysosomes of the muscular fibre (Schwartz and Bird,1977), it is reasonable to suppose that the lysosomial protease plays an important role in the field of the successive autogenic phase to the muscular damage. This supposition is corroborated by the evidence of a strong increase in the lysosomal protease, following exhaustive exercise in an animal model (Vinko et al., 1978). There is also evidence of the fact that the lysosomal enzymes are activated by the increase of the level of intracellular Ca^{++} (Rodemann et al., 1982).

17. The pathway of the phospholipase A_2

The phospholipase A_2 (PLA_2) uses the phospholipidic membrane as an underlayer for the production of arachidonic acid, prostaglandin – in particular the prostaglandin E_2 (PGE_2)-

leukotrienes and thromboxanes. This enzyme is located in the sarcolemma, in the mitochondrial membrane, in the cytosolic compartment and in the lysosomes (Van der Vusse et al., 1989). In particular we suppose that the PLA_2 present in the mitochondrial membrane may be implied in the mechanisms that induce the loss of the homeostasis of Ca^{++} (Cheah and Cheah, 1985). Likewise an increase of the concentrate of intracellular Ca^{++} would involve an activation of PLA2(Vane and Botting, 1987) The arachidonic acid and the lysophospholipids produced by the activation of PLA_2, would cause a destabilization of the membrane structure assuming, in such a way, an important role in the field of autogenic processes following the harmful event (Jackson and Edwards, 1986; Chang et al., 1987). In addition the PLA_2 would contribute to the loss of intramuscular enzymes observable in a muscular injury (Jackson et al., 1987). It is interesting to know that the PLA2 is one of the most important active principals of snake and bee poison. In fact the injection of poison of the coral snake (*Micrurus fulvius*) in the muscle of a mouse, provokes similar damage to that of an eccentric contraction (Arroyo et al., 1987) even if we need to underline the fact that the muscular necrosis induced by the snake's poison is much faster and larger than that seen in eccentric exercise. It is enough to think that an injection of only two micrograms of poison of the Australian tiger snake (*Notechis scutatus*) on rat muscle, leads to the total destruction of fiber in only 24 hours (Harris, 1989). It is also interesting to know that PLA possesses a protective role regarding oxidative stress (Van Kuijk et al., 1987)

18. The pathobiology of muscular lesion

The distinctive element which differentiates a muscular lesion and a lesion at bone level, is represented by the fact that the skeletal muscle heals through a phenomena of "repair", whereas the bone damage heals thanks to a process of "regeneration"- The main part of biological body tissue, at the moment in which it is damaged, heals through a process which hesitates in the formation of a scar area, which represents a biologically different tissue in comparison to the pre-existing one. On the contrary, when a bone segment becomes injured the regenerated tissue results identical in comparison to the pre-existent tissue. The process of repair of an injured skeletal muscle inescapably follows a constant pattern, independently of the cause which provoked the injury itself, whatever the injury may be contusion, elongation or tear (Hurme et al., 1991; Kalimo et al., 1997). In this type of process we may essentially identify three phases:

1. The destruction phase, which is characterized by the breakage and by the consequent necrosis of the muscular fibers, by the formation of a hematoma between the stumps of the injured fibers and by the inflammatory cellular reaction.
2. The repair phase, which consists in the phagocytosis of the necrotic tissue, in the repair of fibers and the contextually production of healing connective tissue, contextual to the capillary growth in the injured area.
3. The remodeling phase, a period during which the maturation of the repaired fibers, the contraction, or the reduction and the re-organization of the scar tissue and lastly, the recovery of the functional capacities of the muscle come about.

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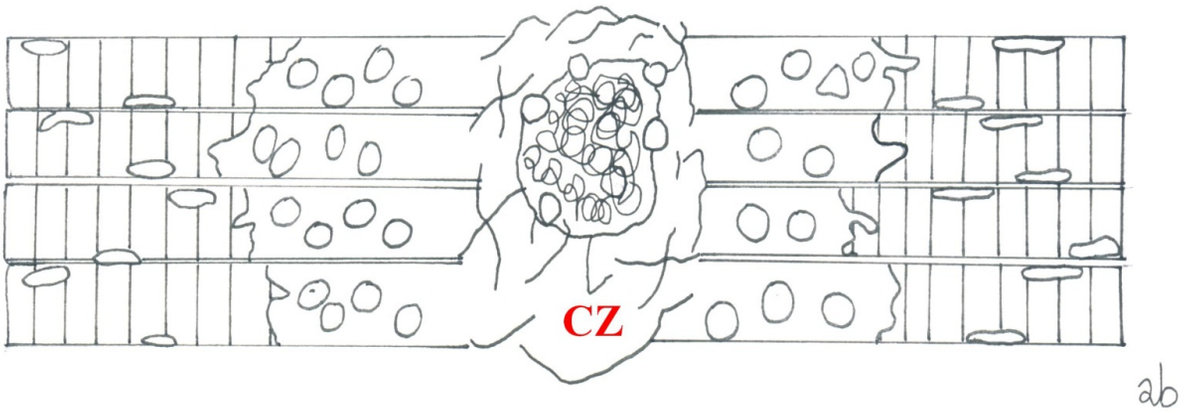
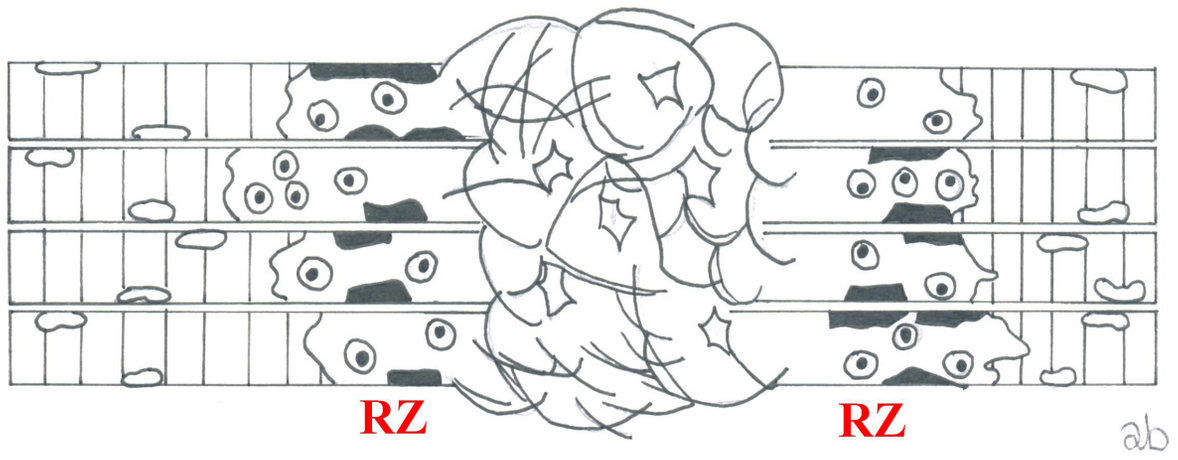
The last two phases, of repair and re-modeling, are usually associated or overlapping (Kalimo et al., 1997).

19. The three post-lesion weeks

The processes of muscular repair are completed in a period of about three weeks during which follow precise and expiring biological stages which we can schematically illustrate in six fundamental phases as follows:



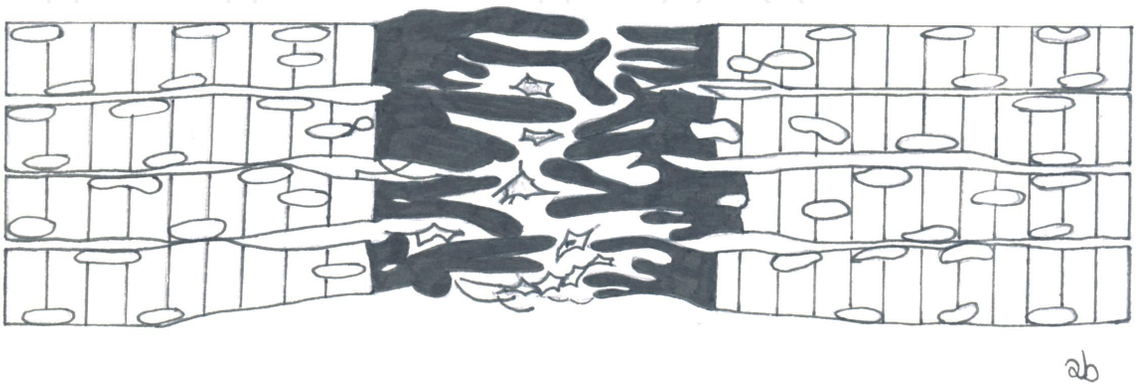
Second post-lesion day: the necrotic parts of muscular fibers have been removed by the macrophages whereas, contextually, the formation, on behalf of the fibers-blasts, of the healing connective tissue inside the central zone (CZ) has started.



Third day: the satellite cells have already started their activation which takes place inside the cylinders of the basal lamina in the zone of repair (RZ).

Fifth day: the myoblasts collect inside the myotubes of the RZ and the connective tissue of the CZ starts to become more dense.

Seventh day: the repair processes of the muscular cells extend outside the old cylinders of the basal lamina up to the CZ area and start to penetrate through the scar area.



Fourteenth day: the healing area in the CZ area is further condensed and reduced in dimension and the repaired myo-fibres fill the remaining gap of the CZ area itself.

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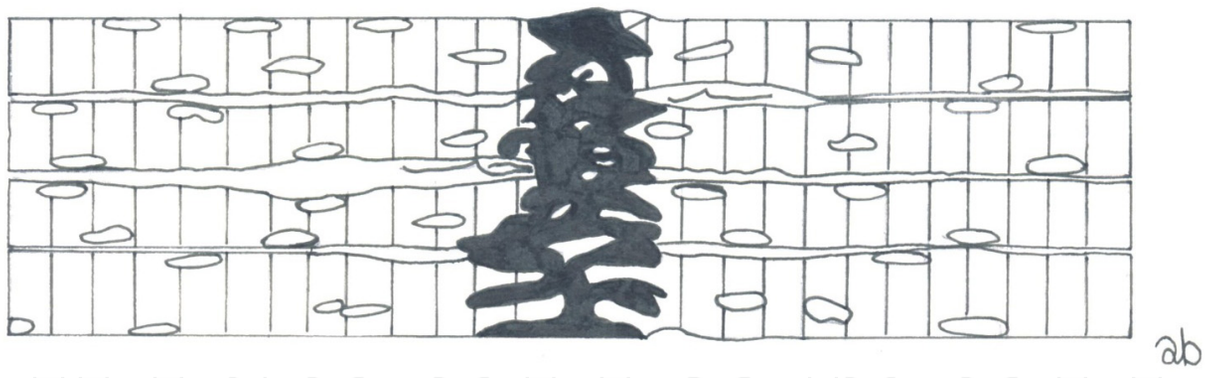

Twenty-first day: the twining of the myo-fibres is virtually complete with the interposition of a small quantity of scar tissue. The quantity of scar tissue is linked to the quality of the repair processes themselves. The remodeling phase of the injured area may lengthen for a period of up to 60 days, depending on the anatomic and functional entity of damage. It is interesting to note that some authors have shown that, in the case which when the muscular lesion extends to more than 50% of the anatomic surface, the complete tissue repair comes about in a period not inferior to five weeks (Pomeranz and Heidt, 1993).

20. The necrosis of the muscular fibre

At the moment in which the skeletal muscle is injured, we can generally observe a mechanical force which extends through the whole transversal section of each single fiber and causes the breakage of the sarcolemma inside the stumps of already injured fibers; leaving the latter amply open. From the moment that the myofibrillars (and consequently the muscular fibers)are, from a structural point of view, cells of notable length and of a lengthened and tapered form, there exists a real risk that the process of necrosis, begun in the location of the injury, extends along the whole length of the fiber itself. However, there exists a special anatomic structure named "contraction band" made up of a particularly dense cytoskeletal material, which behaves as a true "fire door" (Hurme et al., 1991). Some hours following the traumatic event, the propagation of the necrotic process is blocked by a local phenomena represented by a sort of seal carried out by the contraction band on a level of modified areas of the cellular membrane. In such a way, a sort of protective barrier is created inside which starts the repair processes regarding the laceration of the cellular membrane (Hurme et al., 1991). Recent studies have also shown that the lysosomal vesicles found inside the site of destruction of the cellular membrane, cover the role of a temporary membrane and carry out a central task in the healing process of the cellular membrane (Miyake et al., 2001; McNeil, 2002).

21. The inflammatory phase

Contextually into the muscular fiber injury, in the traumatic event, also the blood vessels of the injured muscle tissue are lacerated. In such a way the inflammatory cells, transported by the blood flow, have direct access to the injured site. The inflammatory reaction is "amplified"

by the fact that the satellite cells and the necrotic parts of the injured muscular fibers, release several substances defined "wound hormones", which behave as chemo-attractant increasing in such a way the overflowing of the inflammatory cells (Tidball, 1995; Chazaud et al., 2003; Hirata et al., 2003;). Inside the injured muscle, we may observe macrophages and fibro-blasts whose activation gives origin to the additional chemo-tactic signals (as growth factor, chemiochins and citochines) directed at the circulating inflammatory cells. In addition to this quota of growth factors, produced *ex-novo*, the main part of the muscle tissue contains growth factors stocked in active form inside its ECM, ready to be used in cases of urgent necessity; like for example in the repair of a lesion. (Ragk and Kerbel, 1997). In the case of tissue injury the capacity of biological tissue repair depends on the release of the activation of the growth factors ECM-dependent (or to the growth factors tied to the ECM) and of their capacity to start repair processes (Ragk and Kerbel, 1997). In particular, direct evidence exists that the Tumor Necrosis factor-α (TNF-α) covers and important physiological role in the repair process of the injured skeletal muscle, which is shown by the fact that, if its activity is inhibited during the healing process, there is a slight deficit of the repair capacity of the skeletal muscle itself (Warren et al., 2002). In addition, a large number of growth factors and citochine, as member of the family of Fibroblastic Growth Factors (FGF) of Insulin-Like Growth Factors (IGF), and of the family of Transforming Growth Factors-β (TGF-β), the Hepatocyte Growth factors (HGF), the Interleukin 1β (IL-1β) and the Interleukin-6 (IL-6), are amply known for their expression during muscular injury. After all it is also certain that many other factors, like the Plateled –Derived Growth-Factors are present in the course of various stages which are registered in a muscular injury (Mishra et al., 1995; Burkin and Kaufman, 1999). We should also note the fact that their expression may be induced, in the field of the skeletal muscle by physiological stimuli similar to those which cause micro-traumatic lesions, such as the phenomena of overstretching, or those relative to non-appropriate external mechanical loads (Burkin and Kaufman, 1999; Perrone et al., 1995). Considering the fact that these growth factors make up powerful mytogenic activators for numerous types of cells, it is now an acquired fact that the latter may also be involved in the activation of regenerative processes of the injured skeletal muscle (Burkin and Kaufman, 1999; Best et al., 2001; Chargè and Rudnicki, 2004). A certain number of these growth factors, like FGFs, IGF1, IGF2, TGF-β, HGF. TNF-α and the IL-6,are potential activators of the proliferation of the myogenic precursor cell (MPC,Myogenic Precursor Cells or satellite cells) (Chargè and Rudnicki, 2004). Some of these are also powerful stimulators for the differentiation of the MPC and after, in the course of regenerative processes, regarding the fusion of myotubes in multi-nuclear mature myo-fibers (Burkin and Kaufman, 1999; Best et al., 2001; Chargé and Rudnicki, 2004). In the acute phase, following a harmful muscular event, the polymorphonuclear leukocytes are the most abundant cells present on the injured area (Hurme et al., 1991; Thorsson et al., 1998; Brickson et al., 2001; Schneider et al., 2002; Bricksona et al., 2003) but, before the first day, the latter are substituted by the monocytes. In relation to the basic principles of an inflammatory process, these monocytes are eventually transformed into macrophages, which are employed in proteolysis and phagocytosis of the necrotic material, thanks to the release of lysosomal enzymes (Hurme et al., 1991; Best and Hunter, 2001; Farges et al., 2002 ; Timballi, 1995) The phagocytosis on behalf of the macrophages depending on the necrotic material, makes up a highly specific process. In this phase the intact

cylinders of the basal lamina, surround the necrotic part of the survived cells which have been left intact by the macrophages attacks and which, consequently, will be used as a scaffold inside which the satellite cells, able to survive, will start the formation of new myofibres (Grounds, 1991; Hurme and Kalimo, 1991; 1992). A fascinating demonstration of the incredible exactness and of its high biological co-ordination of this process, is given by the fact that the macrophages, at the same time that they phagocyte the necrotic residue that surrounds the satellite cells, simultaneously send specific survival factors to the satellite cells themselves (Chazaud et al., 2003). It is also important to remember how the trauma involves a contextual breakage of the sarcoplasmatic reticulum and a consequent leakage of the calcium ions contained in it. The drastic increase of calcium ions inside the muscular fiber determines, in the 24-48 post-lesion hours, a reflex contraction of the myofibrils inside and around the injured area. This phenomena involves an auto worsening phase of the injury prolonged in function of the period of muscular reflex contraction due to the phase defined by the name of "calcium overload" (Armstrong et al., 1991a) which we have amply spoken about previously.

22. The role of lactate in the process of muscular healing

A few hours from the injury, the consumption of oxygen at rest, inside the injured muscular area, rises drastically, generating as a consequence an imbalance between the storing and the request of O_2, which in its turn determines a rapid descent in the tension of O_2 inside the injured area. Contextually to this, we assist in an increase in the concentration of lactate inside the lesion. All this series of events is well shown in the process of repair tissue in the ear of the rabbit observed at 15 days from the traumatic event(Hunt and Hussain, 1993) At the moment in which the tension of the O_2 falls, the process of accumulation of lactate starts (Wasserman et al., 1990); to this end it is important to remember that the muscle produces a superior quantity of lactate than that which it consumes, in all conditions, including at rest (Graham et al., 1986). In this physiological context, the lactate assumes a sort of "guide role", inducing the fibroblasts to produce collagen and influencing the macrophages, and eventually also the lymphocytes, to excrete angiogenic substances. The repair components which we could describe as "lactate-guided" would seem to assume an even further importance, above all at the moment in which the inflammatory component diminishes notably, or starting, approximately, from the seventh post-lesion day (Hunt and Hussain, 1993). The accumulation of lactate in the injured area is substantially ascribable to three factors. The first of these is made up of the fact that the vascular damage, following the tissue damage, inhibits the diffusion of O_2 inside the injured tissue, from this follows a quota of lactate which is produced by anaerobic glycolysis (Im and Hoopes, 1970a: 1970b). The second of these, the vascular damage limits the external diffusion of lactate (Hunt et al., 1967) and the last reason, fact which makes up the most important aspect, is the activation of the leucytes which causes the release of a large quantity of lactate, both of hypoxic nature and not (Calwell et al., 1984). The macrophages which appear on the site of lesion a few hours before the harmful event- playing the role of "guided cells" in the field of the first repair processes they are not only able to supply the injured area with lactate, but are also influenced by the quota of lactate present. In fact,

confirming this hypothesis, it is possible to note how the concentration of lactate inside the injured area, diminishes only slightly at the moment in which the concentration of O_2 rises (Hunt et al., 1978). To this end, it is worth it to mention how some authors report values of lactate concentration, inside the injured muscle, between 8 and 18 mmol.1^{-1} (Hunt and Hussain, 1993). On the other hand, the hypothesis, that lactate was implied in the synthesis of collagen, it had already been put forward by some authors more than forty years ago (Green and Goldberg, 1963; Levine and Bates, 1976). In these experiments, it was described how lactate was implied in the synthesis of collagen, the authors noted how in their experiments the fibroblats put into culture, produced a higher quantity of collagen, in comparison with the control group when the concentration of lactate surpassed 20mmol.1^{-1}. In these, just as in other successive experiments of such kind, it was observed in a hypoxic regime, the production of collagen is delayed up until the moment in which the hypoxic cells are not supplied with oxygen. In other words, the production of collagen only starts when there is the contextual presence of oxygen and lactate. This data suggests how the effect of lactate is independent in comparison to that of oxygen (Comstock and Udenfriend, 1970). However, in spite of the first stimulating results, this line of research has been practically abandoned since 1976. After nearly 20 years, other authors speculated that the lactate could work as a regulator in the process of collagen synthesis inside the injured tissue (Hunt and Hussain, 1993). According to these authors, the maximum ratio of collagen production, would occur in the presence of a high concentration of lactate, included between 8 and 18 mmol.1^{-1}, concurrent with an high value of PO_2, equal to about 100 mm Hg. This data, at a first look, would seem paradoxical, since we can usually consider logical a strong presence of lactate where there are scarce conditions of O_2. However, we need to remember that the leucocytes are responsible for the production, in aerobic conditions, for an important quantity of lactate inside the injured tissue area, and that the production of lactate on behalf of the leucocytes inside the injury remains high also in the presence of a high value of PO_2 (Levine and Bates, 1976). This type of biological model, characterized by a high concentration of contextual lactate to a high value of PO_2, would establish a favorable condition, not only to the collagen synthesis but also to the angiogenesis (Hunt and Hussain, 1993) and in addition it is also probable that the lactate serves as stimulus for the secretion of TGF-β in the injured area (Falanga et al., 1991).

23. The repair and re-modeling phase of the muscular fibers

Once the phase of destruction has dropped in intensity, the real repair process of the injured muscle begins, which shows itself through two concurrent processes, which show between themselves, at the same time, complementary and antagonistic: the repair of the destroyed myofibers and of their respective innervations and the formation of healing tissue. A balanced progression of these two processes, makes up an essential pre-requisite for an optimal reactivation of the contractile functions of the skeletal muscle (Kalimo et al., 1997; Hurme and Kalimo, 1991;). In spite of the fact that the muscular fibers are, in general, considered as fibers of irreversibly post-mitotic type, the notable repair potential of the skeletal muscle is guaranteed by an innate mechanism able to reactivate the injured contractile apparatus. Consequent-

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ly, a reserve pool of undifferentiated cells, defined satellite cells are, during the fetal development, dislocated under the basal lamina of each singular muscular fibre (Hurme and Kalimo, 1992; Rantenen et al., 1995; Kalimo et al., 1997;). In answer to the harmful event, these particular cells, initially proliferate, then differentiate into myoblasts and at the end of the process, they connect to the remaining fibers forming multinuclear myotubes. The multinuclear myotubes of recent formation fuse, in a second moment, with the part of the injured fiber which survived the initial trauma (Hurme and Kalimo, 1992). In the end, the part of regenerated myofiber acquires its mature form, with normal streaking and with the myonuclei peripherally dislocated (Hurme and Kalimo, 1992). Curiously, in answer to t very balad traumas, like for example in a singular eccentric elongation which provokes trauma of light entity, the satellite cells immediately respond starting to proliferate, but due to the limitation of trauma and of the rapid "innate" answer of repair on behalf of the fibres of the injured muscle, they auto-block their activation before myoblasts are formed (Aarimaa et al., 2004). In the mature skeletal muscle there exists at least two principle populations of satellite cells (Rantenen et al., 1995; Jancowski et al., 2002; Kalimo et al., 1997; Qu-Peterson et al., 2002;; Rouger et al., 2004; Zammit et al., 2004). The "classic" satellite cells which reside under the basal lamina of the muscular fiber and which can be divided into"committed satellite cells" which are ready to differentiate themselves into myoblasts immediately after the harmful event and the "stem sateliite cells" which have to first undergo cellular division to be able to differentiate (Kalimo et al., 1997; Rantenen et al., 1995; Zammit et al.,2004). Through this cellular division (which may be seen form a biological point of view as a true and proper proliferation process), the population of stem satellite cells, again builds up the reserve of satellite cells for a future possible regenerative request (Rantenen et al., 1995; Zammit et al., 2004). In this population of satellite cells, we may note the existence of and under-population of cells capable of differentiation, beyond the myogenic lines, not only in mesenchymal lines but also in neural or endothelial ones (Jankowski et al., 2002; Qu-Peterson et al., 2002). Up until to today the satellite cells were retained the only resource of the myonucleus in the course of muscular repair (Chargé and Rudnicki, 2004), recent discovery has shown the presence of a different population of multi-powerful stem cells, which can contribute to the reparation of the injured skeletal muscle; the "non-muscle-resident stem cells" (Chargé and Rudnicki, 2004). In fact, even some isolated progenitor cells of the bone marrow (BM), the neuronal compartment, and different mesenchymal tissue, are able to differentiate in myogenic lines. The cells derived from BM, not only contribute to the regeneration of the muscles fibers in the injured skeletal muscle, but they are also able to re-integrate the pool of the satellite cells in the injured skeletal muscle (Labarge and Blau, 2002). In each case, it is important to note that the frequency at which these events happen seems to be very low, also in the case of serious lesion, if compared to the number of regenerated myoblasts derived from the "muscle-resident" satellite cells (Grounds et al., 2002; Labarge and Blau, 2002). So, it is quite disputable the fact that the "non muscle-resident" stem cells may give a significant contribution to the repair of injured skeletal muscle (Ground et al., 2002) In addition to the classic satellite cells, resident in the lower part of the basal lamina, there also exists a distinct population of extra-lamina collocated stem cells, inside the connective tissue of the skeletal muscle (Dreyfus et al., 2004). In answer to a harmful event on the skeletal muscle, these cells take part in the formation of

myoblasts and in the differentiation of myotubes (Chargé and Rudnicki, 2004). After the cylinders of the old basal lamina have been filled with new myofibers, the myofiber itself extends, through the opening of the basal lamina, towards the healing connective tissue, which has been formed between the stumps of the survived myofibers (Hurme et al., 1991; Kalimo et al., 1997). On both parts of the scar of connective tissue, the myofibers and the stumps of the survived fibers, in the attempt to pass through the scar which separates them, form multiple branches (Hurme et al., 1991). After trying to extend, for a short distance, the branches start to adhere to the connective tissue with their final points, forming mini MTJs with the scar tissue. In time, the scar area progressively diminishes in dimension, conducting the stumps to join with each other (Vaittinen et al., 2002). Even so it is still not well known the stumps of the sheared fibers on the opposite parts of the scar tissue, fuse totally between themselves at the end of the regenerative process or if, on the contrary, there remains some form of septum of connective nature (Vaittinene et al., 2002; Aarima at al., 2004). It has also been amply shown how the repair capacity of the skeletal muscle, in answer to trauma, is significantly reduced in the course of life. (Järvinen et al., 1983). This drop in regenerative capacity is not apparently attributable to a drop in the number or of the activity of the satellite cells (Järvinen et al., 1983) but rather to a complex drop in repair capacity of the muscles in an elderly person, such as it seems that each phase of repair process slows down and deteriorates with age (Järvinen et al., 1983).

24. The formation of connective scar tissue

Immediately after a muscular trauma, the gap formed in correspondence with the fibers, is filled with a hematoma, within the first day the pro-inflammatory cells, including the phagocytes, invade the hematoma itself and start to form blood coagulation (Hurme et al., 1991b; Tidball, 1995; Cannon and Pierre, 1998). The fibrin and the fibronectin tie together to form both an initial granulation tissue and an initial ECM, which will serve as a scaffold and as an anchorage site for the successive invasion on behalf of the fibroblasts (Hurme and Kalimo, 1991). We need to remember, to this end, how some fibroblasts present in the granulation tissue, may also derive from the myogenic cells (Li and Huard, 2002). It is very important to underline the fact that this neo-formed tissue bestows upon the tissue of the injured area the initial resistance to be able to support the contraction forces applied to the latter (Lehto et al.,1985; 1986; Hurme et al., 1991c). Following this, the fibroblasts start the synthesis of the proteins and of the proteoglycans of the ECM, to restore the integrity of the framework of the connective tissue (Lehto et al., 1985; 1986; Hurme et al., 1991c; Goetsch et al., 2003). Amongst the first synthesized proteins of the ECM, there is tenacin- C (TN-C) and fibronectin (Lehto et al., 1986; Hurme and Kalimo, 1991; 1992; Goetsch et al., 2003) which initially change direction in multimeric fibrils to then form super-fibronectin, a protein which has much better adhesive properties (Morla et al., 1994; Wierzbika- Patynowski and Schwarzbauer, 2003). Both the fibronectin and the TN-C, due to their elastic properties, are able to support a remarkable number of elongation cycles, in respect to their rest length. These elongations, which are due to mechanical loads applied on a tissue level, play an important role both in the production of force and for the apparition of the first

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precocious elastic behavior on behalf of the neo-granulation tissue of the injured skeletal muscle (Järvinen et al., 2000; 2003a; 2003b). The expression of the fibronectin is later followed by the type III collagen (Lehto et al., 1985; 1986; Goetsch et al., 2003; Hurem et al., 1991; Best et al., 2001; Ground et al., 2002), the production of type I collagen, on the contrary, only starts a couple of days later, to then remain elevated for several weeks (Lehto et al., 1985a; 1985b; Hurme et al., 1991; Best et al., 2001; Yan et al., 2003). The initial ample granulation tissue (i.e. the scar which forms between the stumps of the injured fibers) concentrates a high degree of mechanical efficiency in a particularly reduced area of connective tissue, an area which is mainly composed of type I collagen (Järvinen, 1975; Lehto et al., 1985a; 1985b; Hurme et al., 1991; Järvinen and Lehto, 1993). Despite the diffused preconception that the formation of fibrosis makes up an inevitable process in the natural history of muscular damage (Huard et al., 2002), the increase in the connective intramuscular tissue, in effect, does not increase in a substantial manner in an injured muscle, unless the muscle itself is not completely immobilized for an excessive length of time (Järvinen 1975; Lehto et al., 1985a; Järvinen and Lehto, 1993). The connective tissue scar, which is formed in the injury area represents the weak point of the injured muscle in the immediate post-traumatic phases (Hurme et al., 1991; Kääriäinen et al., 1998); however, its capacity of tensile force, increases considerably with the production of type I collagen (Lehto et al., 1985a ; 1985b; Kääriäinen et al., 1998). The mechanical stability of collagen, in its turn, is due to the formation of intermolecular cross-links, which form during the maturity of the scar tissue (Lehto et al., 1985b). Approximately ten days after the trauma, the maturity of the scar has reached a phase in which it no longer represents the structurally weak ring of the chain inside the injured muscle, so that, if the latter is stretched until break point, the damage generally occurs inside the adjacent tissue rather than where new mini MTJs have been formed between the repaired myofibers and the scar tissue (Järvinen, 1975; Järvinen, 1976; Kääriäinen et al., 1998). In any case, it will still need a long period of time before the strength of the muscle has completely recovered. (Järvinen, 1975; 1976; Kääriäinen et al., 1998). Even though a large part of harmful events on the skeletal muscle heals without the formation of a debilitating fibrotic scar from a functional point of view, the proliferation of fibroblasts can be excessive and hesitate in the formation of thick scar tissue inside the injured muscle. In these cases, which are generally associated with superior levels of muscular trauma, and above all to those which are recurring, the scar can create a mechanical barrier which delays, or sometimes strongly limits, the repair of the myofibers through the gap formed by the damage (Järvinen, 1975; 1976). Some of these experimental studies have recently given interesting clarification regarding the scar formation in the injured skeletal muscle; we have been able to ascertain in fact, how direct application is of a particular form of small leucine-rich proteoglycan (SLRP), of decorin and of an antifibrotic agent like suramin or the γ-interferon, are able to inhibit the scar formation in the injured skeletal muscle (Fukushima et al., 2001; Chan et al., 2003; Foster et al., 2003). The decorin, the suramin and the γ-interferon are all specific inhibitors of the TGF-β (Yamaguchi et al., 1990; Grounds, 1991; Hildebrand et al., 1994; Chan and Foster, 2003) a growth factor which is held responsible for the scar formation during the repair processes of the muscle. In addition to the inhibiting action towards the TGF-β, the decorin and the SLRP, even though they can't tie themselves to the different collagens, are however able to regulate the fibrillogenesis and the assembly of the type I collagen fibrils (Frank et al., 1999; Nakumura et al., 2000; Corsi et al., 2002).

25. The re-vascularization of the injured muscle

A fundamental process in the field of reparation of the injured muscle, is represented by the re- vascularization of the injured area (Snow, 1973; Järvinen, 1976; Józsa et al., 1980;). The restoration of vascularization in the injured area, represents the first sign of reparation and it is a pre-requisite for the successive morphological and functional recuperation of the injured muscle. The new capillary network has origin of the survived trunks of the blood vessels which go towards the centre of the trauma area (Järvinen, 1976) and they go to supply the same area with an adequate amount of oxygen allowing, in such a way, the successive functional restoration of the aerobic metabolism, which represents, in its turn, a fundamental stage in the field of repair process of the myofibers. The young myotubes are supplied with few mitochondria and only show a moderate functional capacity in the field of the energetic aerobic restoration mechanism but they contextually present a clear increase in the energetic anaerobic restoration mechanism (Järvinen and Sorvari, 1978). In any case, during the final phases of tissue repair, the aerobic metabolism makes up the principle energetic resource for the multinuclear myofibers (Järvinen and Sorvari, 1978). This particular repair procedure, also supplies a plausible explanation of why the regeneration of the myofibres doesn't progress further than the precocious formation phase of slim myotubes, up until when the growth of a sufficient capillary network can't assure the necessary oxygen contribution to a satisfying functional restoration of the aerobic mechanism.

26. The regeneration of intramuscular nerves

Similarly to what happens in the course of the process of re-vascularization, the healing of the skeletal muscle may be blocked by a failure in the regeneration of intramuscular nerves (Hurme et al., 1991; Rantenen et al., 1995; Vaittinen et al., 1999; Vaittinen et al., 2001). The regeneration of the myofiber continues from the phase of myotubes formation also in absence of innervations; but if innervations were not completed correctly, a process of atrophy would inevitably occur (Rantanen et al., 1995). In the case of neurogenic denervation, or the breakage of the axon, the re-innervation process requires the growth of a new axon, distally with respect to the breakage area. However, since the moment the axons usually undergo go thorug a breakage inside or around the muscle, the nerve-muscle contact is, generally, rapidly raidly restabilized.

27. The adherence of the myofiber to the ECM

At the moment in which a myofiber loses its continuity also the continuity of the unit "tendon-muscle-tendon" is interrupted at the point of breakage itself and the contractile force cannot be transmitted through the gap which has been created between the stumps of the fibers. In such a situation, in fact, during muscular contraction the stumps are simply pushed further

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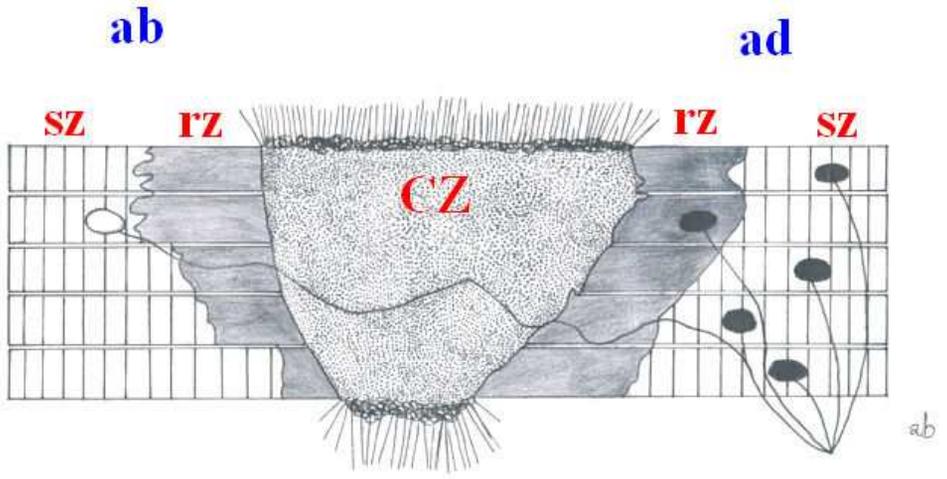

Figure 8. Schematic representation of a breakage trauma of the skeletal muscle. The injured muscle fiber contract and the gap between the stumps, or the central zone CZ; initially begins to fill with the hematoma. The muscular fibers are necrotic inside their basal lamina, of a distance which is usually between 1 and 2 millimeters. Inside this segment generally, with time, complete repair occurs (repair zone RZ; we prefer, in this case, the term "repair zone" to the term "regeneration zone" used by anglo-saxon autors. The reason of this choice derives from the different biological concept between the term "repair" and "regeneration", already illustrated at the beginning of the chapter), whereas in the part of the muscle which is not injured by trauma, we may observe only changes of reactive type (survival zone SZ). Each muscular fiber is innerved, in a single and precise site,by a neuromuscular junction (NMJs, full point in the diagram). Since the muscular fibbers generally break from one or the other side with respect to the line of NMJs of the same fiber, the accessory stumps of fibre 1 and of the fibres that go from 3 to 5, of the "ad" side (right), remain innerved, whereas their accessory stumps on side"ab" (left), remain denerved. At the same time the accessory stump of fibre 2 has remained denerved, because its NMJ is found in the RZ zone. The re-innervation of the accessory stump will come about through the penetration of a new axon sprout through the scar zone in formation (CZ) and so thanks to the formation of a new NMJ (represented by the white point in the diagram). Fibre 2 will go back to its normal re-innervation when the repair process in zone RZ is completed.

aside. The final part of the myofibers in repair which attempt to pass through the scar tissue, maintains a visible growth cone for a relatively long period during the repair process (Hurme et al., 1991; Hurme and Kalimo, 1992), this represents a period of time during which the final part of the myofibers cannot adhere firmly to the scar tissue. However, the myofibers in the course of repair strengthen their adherence to the ECM in both parts of their lateral profile, both in their intact part and in the part of re-growth (Kääriänen et al., 2000; Sorokin et al., 2000; Allikian et al., 2004) (Figure 9), This strengthening of the lateral adherence reduces both the movement of the stumps and the push on the still fragile scar, reducing in such a way the risk of re-breakage and allowing, at the same time, some use of the injured muscle before the healing process is complete (Kääriänen et al., 2001; 2002). It appears very interesting the fact of how mechanical stress is a pre-requisite for the process of lateral adherence, as recently some studies have suggested that they show how the phenomena does not come about in absence of the latter (Kääriänen et al., 2001). In a more advanced phase of the repair process a strong terminal adherence at the end of each stump is stabilized, which consists in the same type of molecule associated with integrin and distrofin that we can observe in a normal MJT (Song et al.., 1992; Kääriänen et al., 2000a; 2000b; 2001; 2002) (Figure9). Contextually, the original (pre-lesion) unit "tendon-myofiber-tendon, is replaced by two consecutive units of "tendon-

myofiber-mini MTJ " type separated by the scar. These two consecutive units contract at the same time, thanks to the fact that both are re-innerved by the same nerve (Rantanen et al., 1995). In the ECM, on a level of the place of the new MTJs, elastic and adhesive molecules are profusely expressed, whose role is to absorb the strength created by the muscular contractions (Hurmea and Kalimo, 1992; Järvinen et al., 2000). At this point of the repair process, having re-established solid terminal adhesions through these mini MTJs, the myofibers no longer need lateral adhesions of strengthening and, consequently, the strong expression of integrin decreases on a level of the lateral sarcolemma (Kääriänen et al., 2000a). The scar gradually diminishes in dimension, in such a way the stumps come close to each other and in the end the myofibers become intertwined, even though, not fully reunited (Kääriänen et al., 1998; 2000a; Vaittinen et al., 2002) (figure9 box C).

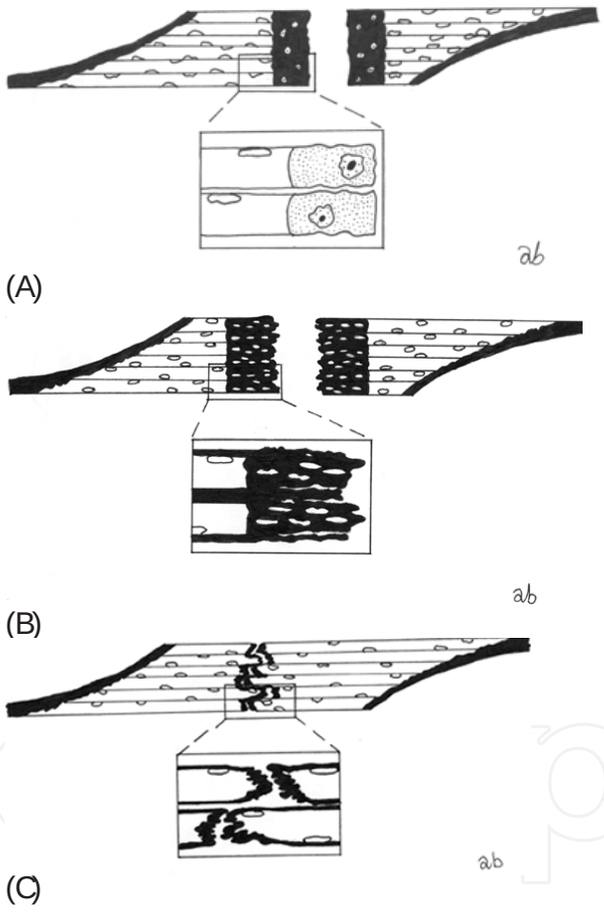

Figure 9. At the beginning of the healing process of the injured skeletal muscle (Box A) the expression of cellular adhesion of the integrin α7β1 molecules is enriched in the terminal part of the fibers of the damaged muscle in regeneration phase, whereas only a small amount of the latter are present in the lateral profile of the myofiber. A dramatic increase in the expression of integrin α7β1 happens along the lateral aspect of the plasmatic membrane (Box B), both in the intact part and in the part in growth phase of the injured myofibers, at the moment in which the muscular fibers in repair phase penetrate the injured tissue. In such a way, the integrin α7β1 supplies stability to the muscular fibers in growth phase which are missing in adhesion in their terminal part. The expression of the integrin α7β1 returns to normal levels in the lateral sarcolemma (Box C) contextually to the normality of the re-distribution of the integrin α7β1 in the terminal part of the fibers in repair, when the latter form new myotendon junctions and adhere to the scar.

http://dx.doi.org/10.5772/56602

28. Conclusions

Today there are only a few clinical studies concerning the treatment of muscular lesions, for this reason the principles of current treatments are mainly based on experimental studies or only on empirical evidence. The experimental studies have shown that the biological basis of the processes that occur during muscle repair are identical regardless of the primary cause of the injury (contusion, elongation or tear). This emphasizes the importance of understanding the basic principles of muscle repair, which represent the essential pre-requisite for a correct approach to the treatment of muscle injuries.

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