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PSYCHO-NEURO-IMMUNE-ENDROCRINE SYSTEM BEHAVIOR IN MECHANICAL TRAUMA

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Mechanical energy is an etiological factor of traumatisms which, in the human being, can produce a local pathology as well as localized systemic acute inflammation as in the case of polytraumatized patients. Acute local inflammation is a process that occurs with vasoconstriction, vasodilatation, exudation, cellular infiltration, coagulation, fibrinolysis and proliferation. These phases of the inflammation can be expressed by the endothelium, although they make up part of a localizing and successive response of the nervous, immune and endocrine systems. In the polytraumatized patients, the ischemia-revascularization, the systemic inflammatory response syndrome, the disseminated intravascular coagulation and the anabolism of the convalescence period would in turn represent the consecutive systemic expression of the nervous, immune and endocrine systems. If injury by mechanic energy produces a consecutive response of the nervous, immune and endocrine systems in the human being, it could be considered that these systems represent the successive expression of functions such as motility, digestion and proliferation which, in turn, are common components of other vital cycles existing in nature. Essentially, the final function that each system successively expresses would be a type of response that has persisted in physiological and pathological situations due to its adaptive effectivity, in this special case, to the mechanical energy.

Sistema psiconeuroinmunoendocrino, comportamiento en el trauma mecánico. La energía mecánica es un factor etiológico de los traumatismos, que en el ser humano puede producir una patología local, así la inflamación aguda localizada, o bien sistémica, como es el caso de los enfermos politraumatizados. La inflamación aguda local es un proceso que cursa con vasoconstricción, vasodilatación, exudación, infiltración celular, coagulación, fibrinolisis y proliferación. Estas fases de la inflamación pueden ser expresadas por el endotelio, aunque constituyen parte de una respuesta localizadora y sucesiva de los sistemas nervioso, inmune y endocrino. En el enfermo politraumatizado, la isquemia-revascularización, el síndrome de respuesta inflamatoria sistémica, la coagulación intravascular diseminada y el anabolismo del periodo de convalecencia representarían a su vez la expresión sistémica consecutiva de los sistemas nervioso, inmune y endocrino. Si la agresión por energía mecánica produce una respuesta consecutiva de los sistemas nervioso, inmune y endocrino en el ser vivo se podría considerar que estos sistemas representan la expresión sucesiva de funciones como son la motilidad, la digestión y la proliferación, que a su vez son componentes habituales de otros ciclos vitales existentes en la naturaleza. En esencia la función final que expresa de forma sucesiva cada sistema constituiría un tipo de respuesta que ha persistido en situaciones fisiológicas y patológicas por su efectividad adaptativa, en este caso particular, a la energía mecánica.

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The interactions existing between psychological, nervous, endocrine and immune processes make it possible to consider that the nervous, immune and endocrine

systems, when studied independently, can be considered components of a single integrated defense mechanism in which the interactions between these systems are so important to understand the adaptation process and the interactions within each system (Ader, Cohen and Felten, 1995).

Mechanical energy, which, transmitted by a solid, liquid or gaseous agent, is the cause of mechanical traumatisms, is an old stimulus of the neuroendocrine and immune systems of the human organism. Mechanical traumatism is a tissular injury that is called contusion if there is no continuity solution. When there is a continuity solution, mechanical traumatisms are called wounds if the soft tissues are damaged and fractures if the bones are damaged.

From a histological point of view, tissular damage is characterized by necrosis, which is a cellular death process in which three phases have been described (Buja, Eigenbrodt M.L. and Eigenbrodt E.H., 1993). The first two phases are reversible (first and second step contusions) and the third phase is irreversible (third step contusion). Cellular death is produced by cell breakage in wounds and fractures. Generally, there is no wound or fracture without an associated contusion, but there may be different degrees of contusion without a wound or a fracture (Figure 1).

The cellular necrosis that occurs in mechanical traumatisms is the stimulus that activates the neuroendocrine and immune systems and that, therefore, gives rise to their integrated response (Barton, 1985). However, the activation of these systems could be a consequence of their own necrosis if both are functionally represented in all of the cells of the organism. This hypothesis could mean that the organism is essentially a neuro-immune-endocrine system that is expressed in different ways. Three forms of expression of this single system could be represented by the so-called control, mediator and structural components. The control component would be represented by the nervous tissue, lymphoid organs and endocrine organs; the mediator component would be made up of the epithelial, endothelial and mesothelial barriers and finally, the structural component would be formed by the muscular-skeletal system, conjunctive tissue and the adipose tissue, that is, structural support and storage tissues (Figure 2).

In the control component, the nervous, immune and endocrine functions are well differentiated and interrelated. Thus, this component is generally used to study the interactions of the psycho-neuro-endocrine-immune system (Ader, Cohen and Felten, 1995). However, in the mediator and structural components, such functions are not so obvious in physiological situations, although they exist, as is verified by the fact that the cells that form them are capable of responding to neurotransmitters, hormones and cytokines, that is, to the molecule signal of the nervous, endocrine and immune systems.

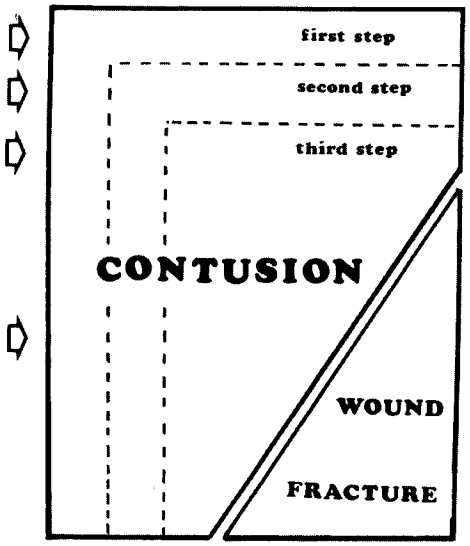

Figure 1. Schematic representation of the types of injuries produced by mechanical energy

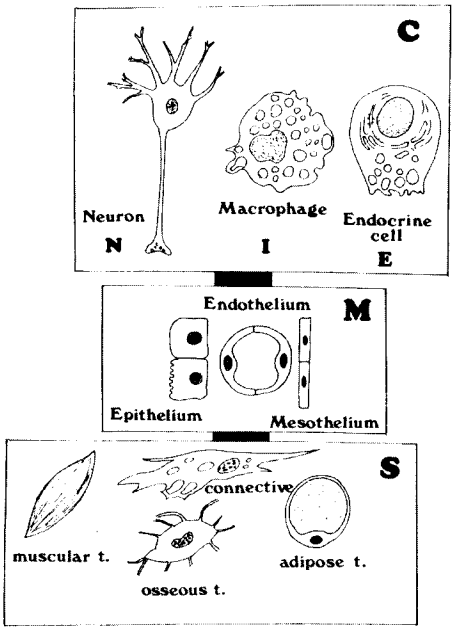

Figure 2. Cellular types which make up the control (C), mediator (M) and structural (S) components of the neuro-immune-endocrine system.

Therefore, the three components mentioned could be considered complementary forms of expression of the neuro-immune-endocrine system and this, in turn, would make up the whole organism (Figure 3a). In this supposition, the post-traumatic necrosis of any site would involve the lesion of the neuro-immune-endocrine system and therefore, its immediate response to injury. In physiological conditions, the nervous, immune and endocrine functions of this single system seem to be balanced, but when a traumatic lesion is produced, one of them successively predominates in relation to the remaining two (Figure 3b). This sequential hyperactivity of the functions may reflect the impossibility of a simultaneous expression of the nervous, immune and endocrine responses to the injury. Thus, this interrelation would vary from a many-fold amplification to the substitution of one response by another.

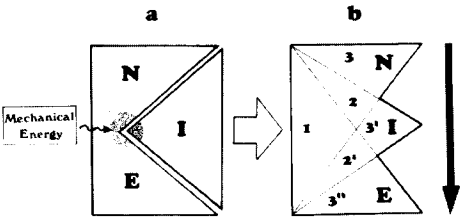

FIGURE 3. a.: Schematic representation of the human organism made up by nervous (N), immune (I) and endocrine (E) systems. b.: The response to injury produced by mechanical energy is successively performed by nervous (N), immune (I) and endocrine (E) systems. The three responses are simultaneously started at a systemic level (1) but they are expressed in successive phases. First, the nervous system (2, 3), then, the immune response (2, 2', 3') and, finally, the endocrine response (2'', 3'').
t:tissue

Necrosis seems to provoke a response that is at first a predominantly nervous one, then an immune one and finally, an endocrine one (Figure 3b). The three responses, although systemic in their origin, are located in the site of the lesion when the stimulus has a small intensity and, on the contrary, has a general repercussion if the stimulus has a large intensity. Thus, the organic response to the injury is proportional to the severity of the lesion except when there is a previous condition that modifies this response.

Local inflammation is the local response to necrosis. This type of inflammation has been studied since ancient times. Celsius enunciated the four cardinal signs of acute inflammation as redness, heat, swelling and pain. John Hunter (1728-1793) was one of the first investigators to make a

scientific study of inflammation. More than 200 years have passed since he stressed the importance of the subject: "This operation of the body termed inflammation requires our greatest attention, for it is one of the most common and most extensive in its effect of any in the animal body" (Lewis, 1978; Lewis 1986).

Different phenomena are successively produced in inflammation: vasoconstriction, which produces ischaemia of the contused tissue, vasodilatation with reperfusion injury (Davis and Hagen, 1993; Entman and Smith, 1994), exudation secondary to an increase of endothelial permeability, which is the cause of swelling (Lum and Malik, 1994), diapedesis or cell migration, especially neutrophils, which is associated with phagocytosis and necrosis (Entman and Smith, 1994), coagulation and fibrinolysis (Davis and Hagen, 1993), proliferation with endothelium and vascular wall modelling (Davis and Hagen, 1993) and tissular regeneration or formation of granulation tissue. The vascular endothelium can play the lead role in these phenomena and successively expresses a nervous or immediate function that is the vasomotor response, an immune or intermediate function, represented by the diapedesis and coagulation, and a late endocrine function that is proliferation (Figure 4). Although factors that are characteristic of the endothelium can play the lead role in these functions, there are "in vivo" extrinsic nervous, immune and endocrine factors that are complemented by those corresponding to the vascular wall to elaborate the systemic nervous, immune and endocrine responses of the acute inflammation, as for example, pain and anesthesia in the early phase, leukocytosis and febricula in the intermediate phase and nervous regeneration in the late phase.

In 1986, Lewis explained the following considerations: "Much of the more recent research on inflammation has been devoted to trying to find the chemical mediators that are responsible for causing the cardinal signs and mechanisms by which they are produced and released. Although this task is by no means completed it has become clear that there are many factors involved and almost all of them in some way alter the activities of the others." Nowadays new mediators are continuously being discovered and new mechanisms are described, but as in other fields of medical knowledge, there is an ever increasing distance between new molecular knowledge and everyday patient care (Böttiger, 1995). It has been shown that the mediators that

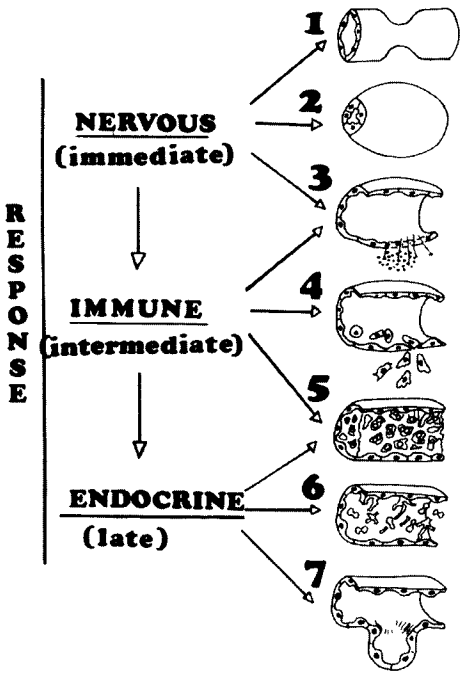

Figure 4. Endothelial inflammatory response. 1.: vasoconstriction; 2.: vasodilatation; 3.: exudation, 4.: diapedesis; 5.:coagulation; 6.: fibrinolysis, 7.: proliferation. The interaction between nervous, immune and endocrine responses avoids the establishment of exact limits between them.

have been described in the inflammation can act in different phases of the response but with different actions. Thus, in the immediate or early phase of the inflammation, nitric oxide (NO) a reactive gas, is synthesized by the endothelium and has a motor vascular function and controls the vascular tone (Anggard, 1994; Kam and Govender, 1994). In the intermediate phase, the macrophages, when they are activated, can synthesize large amounts of NO that are used as a killer molecule and in the late phase, the transforming growth factor ß inhibits the inducible syntase NO (Nathan and Xie, 1994).

Since the successive molecular changes produced in the inflammatory environment are extremely complex, perhaps it would be useful to establish a correlation between the chemical mediators and the clinical manifestations in order to understand the meaning of the local acute inflammatory response.

When the mechanical traumatism produces an intense stimulation of the neuroimmune-endocrine system, as occurs in the polytraumatized patient in which necrosis is associated with shock, death has a trimodal distribution. The first peak occurs within seconds to minutes after injury and is usually caused by lacerations of the brain, brain stem, high spinal cord, heart, aorta or other large vessels. The second peak occurs from minutes to a few hours after injury and generally results from major internal hemorrhaging or from multiple injuries that have less intensity but cause significant blood loss. The third peak occurs several days or weeks after the traumatic event and is almost always a consequence of the systemic inflammatory response syndrome (SRIS) or sepsis (Jacobs and Panic, 1993).

Cardiorespiratory failure is the principal cause of death during the first and second peaks and thus cardiopulmonary resuscitation must be started as soon as possible. The vasomotor response which is produced in this phase is a systemic ischaemia-reperfusion syndrome which is similar to the nervous response present in local inflammation.

The SRIS represents a hierarchical continuum of an increased inflammatory response to infectious and non-infectious stimuli since end-organ dysfunction and mortality increase with each stage of the inflammatory response (Bone, 1995). There is evidence of a clinical progression from the SRIS to sepsis, severe sepsis and septic shock (Rangel-Frausto et al., 1995). The systemic ischaemia-reperfusion and, especially the mesenteric one, also promotes neutrophils and macrophages, which when activated, can provoke distant organ injury (Moore et al., 1994). This immune response has been described in local inflammation. The nervous response in the polytraumatized patient corresponds to the early ebb phase described by Cuthbertson (Cuthbertson, 1942), characterized by hypovolemic and the subsequent sympathetic and adrenal response and the immune response with the flow phase, during which the injured patient loses proteins at an accelerated rate.

During the endocrine response to injury or the convalescence phase the patient undergoes a rapid psychological and physiologic improvement, muscular strength returns to normal and the body weight increases due to the accumulation of body fat and its supporting structure. So, this final endocrine response is anabolic, in contrast to the response produced early after the injury which is mediated by multiple stress hormones (Shaw and Koea, 1993) (Figure 5).

The evolution of the polytraumatized patient could be considered as a succession of three partial responses in which the stimulation of the nervous, endocrine and

immune functions respectively predominates, in which case, it would be similar to that which has already been described in the acute local inflammation (Figure 5). This hypothetical similarity of the local and systemic responses could be attributed to the existence in the organism of a general response mechanism to injury by mechanical energy, which is based on the successive and predominate expression of the nervous, immune and endocrine systems.

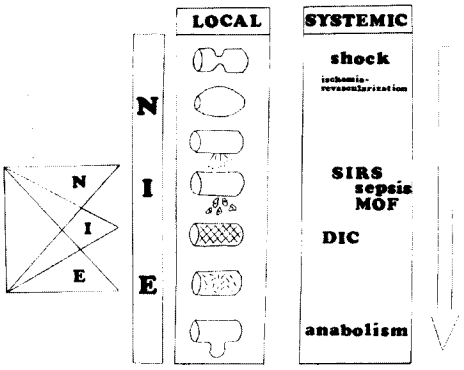

Figure 5. Local and systemic inflammatory response. SIRS: Systemic inflammatory response syndrome. MOF: Multiorganic failure. DIC: disseminated intravascular coagulation

If the systems considered have a functional as well as morphological sequence in their expression in the old biological response to mechanical injury, the latter expression represented in the control, mediator and structural structures, it could be considered that this sequence may represent their evolutionary order. In this case, the phylogeny of this single nervous-immune-endocrine system would imply the consecutive development of the systems that make it up. The oldest system would be the nervous one, the immune system is formed afterwards, and finally, the endocrine system is constituted. Therefore, the systems themselves would mean evolutive phases of a response that, given the antiquity of the stress agent, the mechanical stress, could have already been elaborated in unicellular beings using a common biochemical substrate.

This response that is already represented by the successive activation of the nervous, immune and endocrine systems or by the functions resulting from their stimulation, such as motility-pain, intra and extracellular digestion and proliferation-anabolism has a common duration of eight days in the acute local inflammation, but when it is systemic, as for example in the polytraumatized patient, it can last for several weeks with no change in the meaning of the response. Actually, the motility, digestion and proliferation constitute an an-

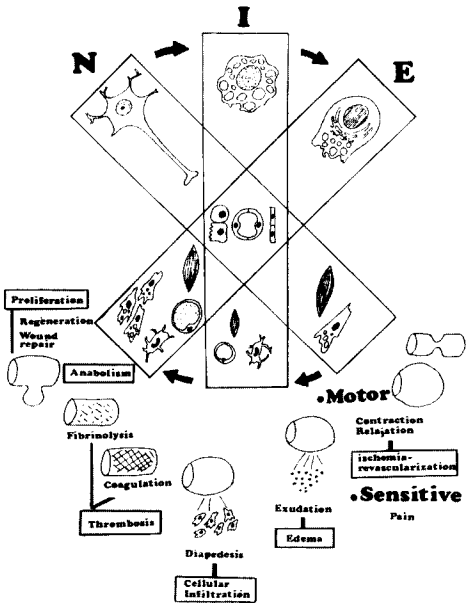

Figure 6. Sequence of the function of nervous, immune and endocrine systems in local and systemic inflammatory response to mechanical stress.

cestral cycle that is not only observed in the pathological responses mentioned but also in the physiological processes such as animal nutrition and in the vital vegetal and animal cycles themselves which are determined by the seasons during a year.

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