Chapter 3

The Skin Neural Interface

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Additional information is available at the end of the chapter

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1. Introduction

The skin is the *smart dress* of all the body and represents its external limit in relation with outside and inside. Due to its particular rich innervations, it plays a basic important role as *polymodal neural interface*. Its structure is made by *three layers*. First the *epidermis* is a pavement epithelium without vessels and in a permanent growth by its germinative stratum pushing new cells to the periphery where the contact with air is drying them generating the stratum corneum of dead cells. That is why only free nervous endings can penetrate the epidermis generating a particular subtle tactile sense. Second the *dermis* is very rich in collagen fibers, vessels, hair roots, sweat glands and sensorial receptors of different types. Third the *hypodermis* has many fat follicles enclosed within fibrous capsules. Below those layers is the gliding *sub-cutaneous tissue* with connective and elastic fibers. Therefore the skin is a *movable dress*, but with some *fixation zones* to the skeleton or to some fibro-tendinous plans like in the palm of the hand or the plantar sole of the foot in order to guarantee safe grasping and locomotion.

It is important to remember that the skin has the same embryologic origin than the nervous system explaining some common physiological and pathological aspects. In fact, the *neural plate* originating like the skin from the *ectoderm* will give later after the development of the neural folds the *neural tube* progressively closed and enlarged at its cephalic end producing the five cerebral vesicles preforming the encephalon. During this embryonic process, the *neural crests* are isolated along the dorso lateral part of the tube to give the *sensory ganglion cells, the sympathetic ganglions*, the chromaffin cells of the *adrenal medulla* of the *surrenal glands* and some *migrating cells* within the skin described as *Langerhans* or dendritic *Merkel* cells responsible for *acquired immunoprotection*.

Finally the *smart transducer skin dress* allows to define five different and complementary functional neural interfaces: exteroceptive, proprioceptive, interoceptive, homeostasic and regenerative.

2. Exteroceptive neural interface: the multimodal contact

2.1. Touch and palpation

The skin can receive tactile information from the environment with contact of different pressure mode going from the light skimming touch due to the free epidermic endings till the deep pressure on the subcutaneous organs. It can also use their sensorial detectors to make contact with objects and move a sensitive skin surface to detect and identify the physical qualities of any structure defining the haptic function possibly assimilated to a cutaneous eye. Pain and temperature sensing are referring to other structures.

A. The encapsulated cutaneous mechano-receptors

A great deal of work has been done to characterize the different types of sensory receptors using physiological experimental techniques like microneurography and microneurostimulation as well as histological studies with the precious help of the electronic microscope. That means that we have at the present time a precise set of data concerning morphology and function of those receptors, but still a lack of complete understanding of the integration within the central nervous system of all types of sensations. Two functional types have to be considered: slow adaptating (SA) activated during all the duration of the stimulus and fast adaptating (FA) answering at the initiation and at the end of the stimulus. The richness of the skin sensitive matrix is also linked to the topographic repartition of the receptors in superficial and deep parts.

A.1. The epithelial Merckel discs: (SA I)

They are the smallest in the order of 2μm and placed parallel to the surface in the stratum germinativum or close to a hair follicle. The cell contains osmiophilic grains in relation with a neurosecretion and its surface is attached to keratinocytes by desmosomic links. They could be grouped in corpuscles or in Pinkus complexes and a single neurite can transfer information of few corpuscles. They do not have rest discharge and can give indication about the direction of the mechanical stimulus. It is important to make distinction between this mechanoreceptor and the dendritic cell also called Merckel and responsible for acquired immunoprotection.

A.2. The Meissner corpuscles: (FA I)

With an ovoid shape and a long vertical axis of 150μm, they are made by a superposition of Schwann cells between which are passing afferent interlaced fibers. Located mainly within the pulp of fingers, palm and plantar sole, they are sensitive to the direction, intensity and velocity of the mechanical impulses.

A.3. The lamellous Pacini corpuscles: (FA II)

They are the largest receptors in ant eggs shape of 2 to 3mm diameter and in fact visible with the naked eye. They are located in dermis and hypodermis of hand palm and plantar sole as well as in abdominal cavity and external wall of some big arteries and we will discuss later about their important functionnal role as pressure transducer. At the central part of the fifteen to thirty connective lamellas creating the classical aspect in onion bulb is a neurite with a neural plate. In addition some microarterial capillaries circulating between the lamellas are responsible for the renitency of the receptor and therefore for its sensibility. That can explain the balance perturbations in diabetic patient suffering of diverse microangiopathy changing the Pacini threshold.

A.3.1. The automatic regulation of the grasping force:

That is an interesting neurophysiological aspect of the automatic control of motor functions related to the existence of a concentration of Pacinian corpuscles in the palm and palmar aspects of fingers. We studied this phenomenon in our biomechanical research unit using a cylinder test equipped with strain gauges in order to measure the grasping force as well as the acceleration. When a person is grasping by placing its palm around this unknown object and of course with unknown weight, the grasping force is generally higher than the minimum required. A second grasp of the same object shows a regulation with adaptation of the grasping force. If we increase progressively the weight of the object during the grasping phase by filling it with lead powder the force is normally increasing in relation with the variation of the weight. But we made this test in different categories of subjects and observed two extreme functional profiles: those who increase the force with a curve parallel to weight variation and those who have no regulation at all with a great initial level of force without change in relation with the weight variation. We also asked to the subject to voluntarily decrease the grasping force until the sliding of the object and we saw that a certain but variable safety margin exists to guaranty a safe grasp. That allowed us to identify the great differences between individuals regarding the precision and quality of regulation of this grasping automatic control. We established also a link with the important variations of the number of nervous fibers within the peripheral nerves and particularly in the upper limb and the hand. The mean number calculated on the counting fibers on cross sections of the nerves using a silver impregnation to visualize the myelin sheath in the different parts of the brachial plexus on 20 different cadavers was of 110000 fibers, but the individual variation on our sample was going to double or triple. The conclusion was that it is no equality among people regarding the quantitative aspect of the neural equipment not only in the peripheral nervous system but also in the central nervous system. That can also explain partially the inequality of mental aptitudes among individuals.

A.3.2. The plantar force plate and the body balance regulation:

That is another interesting example of the mandatory automatic control of balance in vertical posture in relation also with the Pacinian corpuscles. Therefore man is the pilot of a very complex machine and in most of the case he is almost completely ignorant about its own anatomy and neurophysiology. Moreover the one who knows anatomy and neurophysiology is not functioning better that the ignorant pilot. That means that everything is made in the human construction plan to simplify at the maximum the conscious decision and command of action and to made unconscious the very complex technical problems to solve for the execution of motor tasks. The vertical posture on two feet (bipodal) or one foot (monopodal) is a good example of this full automation of a complex motor function. What we have to call the *postural servomechanism* has inputs and outputs.

The three inputs: visual, cutaneous and vestibular are redundants:

- the *visual input* takes unconsciously a vertical or horizontal reference line in the space and can alone achieve a stable balance. We demonstrated in our center that putting a person in a room without linear references create some specific optical vertigo, that it is also possible to reproduce by projecting in a dark room an inclinated line taking as a false reference by the person and generating a particular sensation due to the discordant perception of visual and cutaneous inputs.
- the *cutaneus input* is made by a string of corpuscles of Pacini located in the deep part of the plantar sole all along the ground contact part of the skin. They can detect the disequilibrium of the vertical posture on the two axis antero-posterior and lateral. This input is also able alone to assure a correct balance. Normally closing eyes in vertical position do not perturb the balance which is the case of blind persons. But in certain neurologic disorders like tabès characterized by a lesion of the posterior funiculus of spinal cord conveying the information of Pacini corpuscles, the equilibrium is impossible without the vision. This clinical test was described by Romberg.
- the third input is *vestibular* with the activation of the two accelerometers: angular with the three semicircular canals oriented along three orthogonal planes and linear with the utricular macula which is a gravity transducer allowing to maintain the head in horizontal position and the sacular macula for transversal movements of the head. The vestibular system is a complex accelerometer using a liquid technology with two liquids: perilymphatic and endolymphatic which also exists in the cochlea responsible as frequency analyzer for hearing, a completely different function, but with a common technical problem of precise osmotic regulation of those liquids. That can explain why vestibule and cochlea are linked in the same anatomical structure, the ear. Therefore the vestibule has a threshold as well as an inertia responsible for a remanence after stopping a movement. Only the vision can stop the vestibular activation avoiding a vertigo by resetting the transducer. In fact the vestibule in vertical posture can generate large oscillations for corrections in case of movements beyond its threshold. But its major role is to give a 3D trajectory for walking or running without vision.

The outputs are automatic muscular contractions by impulsions for correction of the disequilibrium in two directions. An EMG recording of anterior and posterior muscles of the leg and simultaneous recording of the center of pressure on a force plate can show clearly the proportionality of the muscular contraction with the importance of the disequilibrium in the limit of the 7° of acceptable oscillations of the whole body. These investigations are commonly done by the medical and non medical practitioners in posturology. An important literature can be seen on this modern topic.

A.4. The Ruffini corpuscles: (SA II)

They are *mechanical traction transducers* due to their elongated structure of 2 mm long with inside collagen fibers included in a liquid, surrounding a nucleus and with a thin capsule open at the two extremities. That allows some collagen fibers to go out and to be anchored and integrated within the chorion, making the corpuscles very sensitive to the mechanical deformation of the skin. A nervous fiber is penetrating within the corpuscle at its middle part and distribute fine ramifications inside. The neural reception field is large. This structure is very similar to this of the neurotendinous Golgi organ and play a great role in the body position and movement sense that we will talk about later.

A neurophysiological problem which did not find until now its solution can be called: sensorial convergence. In fact they are more receptors than afferent fibers to convey the information to the centers. For example looking at the finger innervations shows a great quantity of mechanoreceptors and largely less sensitive fibers within the two median and ulnar nerves. We have seen that several Merckel discs can corresponds to only one neurite, but for the other corpuscles the ratio 1/1 is the rule. The point is to know if different corpuscles types can be linked on the same fiber or if different topographical levels of same receptors can be associated. Presumably the answer has to be found in the organization of the somatotopy of thalamus and cortex identifying the different neuronal fields and their functional specificity. Anyway the Weber test exploring the identification of two separate contact points is in direct relation with this problem because the perception of a double contact is directly linked with the stimulation of two different neuronal fields. In addition a normal overlapping of perception fields exists and it is needed to get a complete anesthesia of a skin territory to cut three successive sensitive roots corresponding to three dermatomas.

B. The temperature and pain receptors:

Even if the two systems are specific, they are closely linked within the central nervous system. The temperature sensing is in relation with free endings with dilated end in cone or bulb shape in epidermis and mainly dermis. They are originating from Aδ myelinated fibers of small caliber of 5μm for cold and C amyelinic fibers of 1,5 μm for warm.

Regarding pain, the technical problem seems to be more complicated. Pain has to be considered basically first of all as a *protection system* generating a priority signal travelling as fast as possible within the nervous system in order to induce withdrawal reflexes or shunning reactions. This important *alarm system*, existing in all animals, requires a precise location of the injured part of the body to adjust the protective answer in the best possible conditions. That means a mandatory projection on the area 3 of the somato-sensory parietal cortex. On the other hand, specific nociceptors made by Aδ and C fibers were identified with slow conduction.

Therefore the question is to know if a supraliminal stimulation of a mechanoreceptor can generate a pain signal or if it is needed to think that a normal field reception is doubled by a nociceptive field ? presumably the truth is between. For example pinching the skin create a specific sensation which become painful if the pinching forces are stronger or putting a hand under water allows to identify the temperature of the water which can also become painful if increasing too much. That anyway allows to understand why temperature and pain are linked in the same central pathway and also the existence within the dorsal horn of the spinal cord of two types of nociceptive neurons. The first category is the specific nociceptive neurons which are located only in the layer I and have a little receptive field without overlapping. The second is the convergent neurons or also called WDR cells (wide dynamic range) or trigger cells or multireceptive neurons which are mainly within the layer V, have a large overlapping receptive field and are able to generate sensitive summation phenomenon explaining some projected pain like in arm in case of angor or in testicle in case of nephritic colic. Those convergent neurons have also a peripheral zone able to generate inhibition by non nocive stimulation. In addition to the neuronal activity, it is important to mention a very rich neurosecretion like excitatory aminoacids (glutamate or aspartate) or inhibitory like GABA or neuropeptides like substance P, enkephalin, somatostatine ...

2.2. The central neural pathways

Two different systems are corresponding to the two different aspect of tactile sensation.

The first is called *epicritic sensibility* and characterize a *precise body localization* and functional identification in relation with *touch contact discrimination, goniometric* and *statokinetic sense*. The signals are travelling within the dorsal column of the spinal cord along the *medial gracile fasciculus* for lower limb and abdomen and *lateral cuneate fasciculus* for upper limb and thorax to reach the two corresponding nuclei in the medulla. Then the fibers after synapses are crossing the mid line to create the *medial lemniscus* going to the *thalamic ventral posterolateral nucleus* in its pars oralis (VPLo). From the thalamus which is the convergent system of all the sensibilities except the olfaction, the fibers are projected on to the primary somatosensory cortex located on the parietal post central gyrus with the specific area 1 and 5 for the body scheme which is cutaneous and not muscular, area 3 for a precise body localization and area 2 for statokinetic perception (position and movement) including the segment goniometry. It is possible to find on the post central gyrus the same disproportional topographical representation identified by cortical electrostimulation on awake patients made by the Canadian neurosurgeon Penfield (motor and sensitive homunculus).

The second system is called *protopatic sensibility* and concerns *temperature, pain* and *crude touch* conveyed by Aδ fibers articulated in the posterior horn with lamina I and IV and V (nucleus proprius) and C fibers with lamina II and III of the substantia gelatinosa and VII and VIII. Then they travel within the dorsal and ventral *spinothalamic tract* (extralemniscal way) which is placed in the medulla and pons laterally to the medial lemniscus with whom its reach the thalamic ventral postero-lateral nucleus (VPL) in its pars caudalis for the ventral tract and in its pars posterior for the dorsal tract. In addition to the spinothalamic tract representing the alarm system mentioned before is the spinoreticulothalamic tract containing mainly C fibers which goes to the medullar, pontine and mesencephalic nuclei of the reticular formation (17 identified separate nuclei) and periaqueductal gray matter (rich neurosecretion within LCR). Finally this tract reach the reticular nuclei of the medial thalamus (intra and parafascicular) and then the anterior cingulate cortex (area 24) and close prefrontal cortex. That explains the two specific part of the pain sensations: first the *alarm system* well localized in the body with a discrimination of pain origin (stinging, cutting, burning ...) and second the *emotional component* possibly going to the *suffering* in case of chronic pain. Finally the central control of pain is made by three centers:

- the *spinal cord posterior horn* connected with the spinal ganglion which is the first pain processor unfortunately unknown by most of the spine surgeons operating on the vertebral disc. Some active inhibition process described by Melzack and Wall in 1965 as the *gate control theory* concerns the possible action of skin large fibers Aβ on the neurons of the substantia gelatinosa closing the door of the spinothalamic tract. That also can be done surgically as demonstrated by Marc Sindou.
- the *reticular formation of the brain stem* responsible for neurosecretion and activation/inhibition for ascending and descending pathways with three columns: *medial* with the 6 raphe nuclei with an important neurosecretion mainly serotonin, *central* with 5 nuclei in relation with motricity and *lateral* with 6 nuclei related to afferences. Even if we know precisely the morphology of those nuclei, more scientific investigations are needed to understand completely their specific functional activity.
- the *selective filter of the thalamus* in which 70% of the relay neurons of the VPL and VPM receive cutaneous inputs with roughly 20% of nociceptive specific neurons, 30% of low threshold mechanical SA and FA receptors and 50% of convergent WDR neurons in relation with non-noxious and noxious stimuli. The large diffusion to all the cortical areas of the pain signal is depending first to its localization by area 3 of the parietal post central gyrus.

3. The proprioceptive neural interface: The skin goniometer

As defined by Sherrington, the proprioception is the self sensibility of the body. In other words, the stimulus is not coming from outside but from inside of the body. That concerns essentially the perception of position and movement of all parts of the body. We have done in our research center many investigations on robotics and have had the privilege to cooperate with industry and particularly with the French Renault car factory which started its industrial robotic activity in 1974.

In order to better understand the technical problem in human, we will use a robotic model:

3.1. The robionic model

We created the term of Robionic in 1992 at the occasion of a robotic symposium in Singapore. That concerns the association of robotics, biology and electronics and was more appropriate than the term of bionics used in the sixties by the americans. At the present time, the engineers are talking about mechatronics. The name robot which means work was introduced by Karel Tchapek in 1922 in its theater performance called "the Universal Robots of Rossum". An industrial robot is a manipulator with several degrees of freedom (DOF). Some, considered as intelligent, are equipped with artificial sensorial systems, vision and tactile sensibility, allowing them to be adaptable to the unpredictable variations of a provided technical programme. The human limbs are also polyarticulated systems with many DOF and it is acceptable to stipulate that the control problems of human joints are of the same nature than the control of a robot, with of course some important differences regarding the type of actuators and the structure of the mandatory transducers. Two interesting transfers of knowledge can be taken in consideration:

A. From living to artificial

that is concern with the possible mimic of some living systems (biomimetism) like for example the compound eye of the fly which has 3200 optical microunits called ommatidies having a little lens as well as neural substrate with some specialized units in the detection of a particular direction of movement. The neural integration of the visual information is particularly complex but give to the fly a fantastic instrument to detect movement of objects or optimal trajectories for flying. Unfortunately a posterior dead angle of 7° make possible to catch it even if its reaction velocity is superior to man. A research team of Marseille was using this technology to design a special visual polydirectional transducer for mobile robot. Another example of biomimetism is the copy of articulated legs of animals to design legged machines including the present bipedal robots developed particularly in Japan for home services.

B. From artificial to living

this transfer is more interesting for us to understand the technical problems of human motor control. In fact to drive the terminal organ of a robot in a 3D space in order to grasp and manipulate objects, it is mandatory to find the correct algorithm of command and write the complex equations for that. Two basic information are needed: the state of the motors and the angulations of joints. In industry, the motors are commonly or electric or hydraulic. In both cases, they are reversible by inversing the electrical current or changing the hydraulic pressure. That means that the state of the motors can be identified by the measurement of the intensity of these two parameters. Regarding the angulations of the joints, it is easy to measure it by using linear or angular potentiometers placed on the axis of the joint and all possible forms and resolution commonly exist in the numerous catalog of components. It is now interesting to transfer these notions to the human manipulator control.

3.2. The human motor control

first of all, it is important to analyze the differences between the human manipulator and the industrial. It is also a polyarticulated structure, but in general with largely more DOF: 2 to 6 for a robot and until 31 for the human upper limb (9 for shoulder/arm/forearm/carp and 22 for hand). Concerning the actuators, muscles are viscoelastic, non reversible and non linear. That means that two actuators are needed for a single DOF: agonist and antagonist which is more complicated than the reversible industrial motors. They are roughly 600 muscles actuators in the body. The force is given by the shortening potential of the muscular fibers which cannot exceed one third of the length explaining the mode of construction of the different muscular plans which cannot be built using the best mechanical conditions. The viscoelastic structure of muscular fibers is made by the repetition of two components: a black disc made in contractile protein like actino-myosine able to reduce the length and a white disc made in elastin allowing a great flexibility and good absorption of mechanical stresses. For this reason the whole system is called striated muscle. It has the great advantage to be able to move without noise which is not the case for industrial motors.

The *motor command* is based on the concept of the *motor unit* representing the number of muscular fibers activated in on/off mode by a single motor neuron. Therefore the value of the different motor units is not uniform. In a muscle moving the eye ball they are 25 muscular fibers for a motor neuron and in the muscle on which we are sitting the great gluteus muscle around 6000 fibers for a motor neuron. That explain one of the basic rules of the organization: the *proportional control* by a variable *recruitment* of new motor units in relation with the type of motor task and the force requirement precisely controlled by the central nervous system and particularly by the cerebellum. In addition, the central nervous system has to know for an appropriate motor control the two pertinent information mentioned before for robot: the state of the motors and the angulations of joints:

A. The state of the muscular actuators

they are three possible states of muscles: relaxed, contracted, stretched. The sensitive parameter in this measurement is not the length as some physiologists still believe but the stiffness. This point is particularly important to be correctly understood. Therefore the optimal transducer is the *muscle spindle* made by few small striated fibers placed in a fibrous capsule attached to the muscle. Its length is in the order of 1 cm which make possible its microdissection under microscope. The intrafusal muscular fibers are innervated by gamma motoneurons entering at one of the extremity and giving the sensibility of the transducer. Sensitive neural fibers type Ia are fixed on the muscular fibers: at their equatorial part for the annulo-spiral fibers and middle part for the "en grappes" endings. Those nervous fibers are reaching the anterior horn of the spinal cord as fast as possible using a monosynaptic junction with the alpha motoneurons responsible for the contraction of the extrafusal muscular fibers of the muscle concerned. In fact when pulling a muscle with a traction on the muscle spindle, a muscular reflex contraction occurs which is called *myotatic reflex* (or stretch reflex of Sherrington). This basic reflex is not made only for exploring the motor control using a hammer with percussion on tendons like the neurologists are commonly doing, but it is the basis of the peripheral adjustment of the level of force needed to achieve a particular task. The decision of action initiated within the premotoric area of the brain is followed by the right choice of actuators made by a cortico-cerebellar loop, the right balance between agonist and antagonist controlled by the intermediate cerebellum and the correct level of force determined by the muscle spindles. The activity of the gamma motoneurons regulate the tension of the intrafusal muscular fibers explaining a possible hypertonia or hypotonia. In addition the inferior olive, a great nucleus of the medulla in pleated cortex shape, is playing the role of a corrector of errors in real time thanks to their connections with spinal cord and cerebellum.

All the muscles have muscle spindles except the vocal cord which is vibrating at high frequencies (20 to 20000 Hz) and is controlled by the hearing function and facial muscles responsible for mimics which are included within the facial skin and controlled by the trigeminal nerve in charge of the sensibility of the face. The ocular muscles and the lombrical muscles of the hand are very rich in those proprioceptors. Obviously in normal conditions, the myotatic reflexes are controlled by the central nervous system (spinal cord, brain stem and cerebellum). For example doing flexion of the forearm on the arm requires to inhibit the reflex on the triceps muscle (reciprocal innervations) allowing the biceps to move freely. That explain the *spasticity* which occurs in paralyzed patients by spinal cord injury, which made difficult the mobilization of the joints due to the lack of reciprocal inhibition of the myotatic reflex. In certain clinical cases the spasticity can be helpful like for standing up. But it can create, in the upper limb, spastic contractions in flexion with progressive fibrosis of the muscles.

B. The angulations of the joints

according to what we demonstrate before, the muscle spindles cannot measure the length of the muscles and even so, it doesn't exist within the brain a library of all the muscle skeletal insertions with the distance to the rotation axis of the joint allowing by a geometric calculation to know the joint angle value. In addition we commonly represent the muscle by a vector made by an arrow with a direction and an intensity which is a typical human language not understandable by the brain. The ligaments as well very rich in mechanoreceptors are not able to measure angle joints because they are not extensible and are redundant like in the carpal joint. They have to be considered as joint movement limit indicators, which explain painful sprain in case of over traction of the joint. The interesting solution is to use skin as a goniometer. In fact, they are many Ruffini transducers in the periarticular skin which have the same histological structure than the Golgi organ and are sensitive to the mechanical deformation of the skin of all the body segments in position and movement. The skin is movable thanks to the subcutaneous connective tissue but fortunately also fixed to skeleton and some tendinous sheaths like in the palm or plantar sole of the foot.

This important goniometric role of the skin can explain why the motor key board of the area 4 in the precentral gyrus is very close and linked with the sensitive key board of the areas 1,2,3,5 of the post central gyrus, generating a close loop control regulation that we called stato-kinetic loop. The same disproportional representation (homunculus) of muscles and skin territories exists in the two key boards, as demonstrated by Penfield after cortical electro-stimulations on awake patients. A great face corresponds to mimics and speech. A large hand with a great thumb is in relation with grasping function. A little lower limb representation is placed in the interhemispheric fissure presumably due to the automatic control prevalence of this limb, which also explain the relatively fast restoration of some form of walking in patients after stroke. The hemi-negligence syndrome, observed in hemiplegic patients, is in reality an alteration of the sensitive key board perturbing the position and movement sense. In normal conditions, this stato-kinetic loop allows precisely to know where we are and where we go at any time.

Some experimentations can also demonstrate the cutaneous goniometry by anaesthetizing periarticular skin territory. In this case, the person cannot precisely localize in 3D space without vision a segment of the body, like we observed for ankle joint and finger joint. On neurophysiological point of view, that reinforce the idea that muscles cannot give angulations' data, even if some physiologists reported projections of muscle spindles output on area 5 of the somato-sensory cortex.

They are also pathological arguments to validate that. The paraplegic patients with complete spinal cord functional section have no sensibility and they cannot perceive consciously the position and displacement of their lower limbs. That is called *asomatognosia* which can also be noted in tumors located in the parietal lobe. The patients are not paralyzed and can move freely upper limbs, but without vision they cannot identify position and movement of limbs. In addition, the post surgical scars particularly on knee, abdomen and back spine can disturb the skin goniometer and require some special resetting rehabilitation techniques in order to suppress pain or motor functional disorders sometime in the contra lateral side.

Finally, the *body scheme* that we have normally in our mind is not in relation with muscles but with skin and vision. As we mentioned before, muscles are consciously perceived only when they are painful in relation with C fibers between muscular fibers called metaboreceptors, corresponding to their sensibility to chemical factors like lactic acid accumulated after strong muscular exercise. We also command voluntarily and consciously movements and not muscles and we doesn't need to know we have muscles to achieve very complex tasks.

4. The interoceptive neural interface: The visceral mirror

The viscera placed within the thoraco-abdominal cavity are controlled by the vegetative nervous system with the two sympathetic and parasympathetic polarities on an unconscious automatic mode. Therefore their functional disorders can be expressed by clinical symptoms among which pain is the most frequent. But according to the poor conscious perception of viscera due in great part to the impossibility to feel or see them, the pain alarm of clinical disorders logically is projected on skin, which is on the contrary very precisely accessible for the people. Therefore it is classical to describe painful sensation in the right abdominal fossa in relation with appendicitis, right scapular pain with gall bladder problem, lumbar pain with nephritic colic, left abdominal fossa with sigmoiditis, left arm with coronary infarct... Anyway that not excludes real pain of internal organs like ureter, urethra, bronchus or Fallopian tube. But the close relationship between skin and viscera is a reality that Henri Jarricot (1971) was demonstrated by the technique of "palper-rouler" which is to pinch abdominal skin fold to detect a specific metameric pain corresponding to a particular viscera. He made a precise map allowing also by skin manipulation (reflex dermalgia) in the most painful area to get good clinical result. For example, making this manipulation on the area of gall bladder placed on the right part of the abdominal wall below the last ribs and using at the same time a stethoscope to listen the middle abdomen allows to perceive the contraction of the gall bladder and its expulsion in the duodenum with pain loss. The same maneuver can be done on the skin of left iliac fossa to treat the typical pain related with colo-sigmoid spasm. The modification in those areas of the tactile perception of the skin is related to oedematic infiltration by activation of sympathetic and C fibers which are connected with the vegetative visceral intermediate zone of the spinal cord. That is also important to know in order to avoid diagnostic mistakes.

5. The homeostasic skin: The neuro-vascular bundles

This functional aspect of the skin has some specificities which are not well known even if some recent scientific work has demonstrated the physical, histological and physiological reality of neuro-vascular bundles that Chinese called long time ago acupuncture points. This ancient technique is more and more used in medicine and a new scientific orientation of research allows to modify the Chinese tradition in order to make it more acceptable by modern medical community. Niboyet in 1963 demonstrated the less electrical resistance of the acupuncture points which was confirmed by a series of measurement made in direct and sinusoidal current by Terral in the Unit 103 of INSERM in Montpellier. The use of a curve plotter and of an exploratory electrode equipped with a force strain gauges bridge allows to record very precisely the relation between pressure on the skin and electrical equivalent circuit changes corresponding to low electrical resistance in the order of 10/560 kΩ. A first hypothesis to explain this phenomenon was to think about a skin surface effect related to a secretion of sweat glands as pointed out by some researchers. But the persistence of the current modification after cleaning the skin with ether/acetone and similar positive test on the skin of fresh cadavers obliged to predict a specific subcutaneous structure.

An *histological study* was performed by Terral and Auziech in 1975 in the faculty of medicine of Montpellier. Before operating on serial histological sections, the point electrically localized was injected with black ink in order to be sure of its precise localization. Then different staining methods were used (Coujard-Champy and silver impregnation) allowing to identify what were called "neurovascular bundles" (NVB) with, visible on serial sections:

- lax connective tissue with a shaft in the dermal layer
- different types of cell: fibrocytes, fibroblasts, mastocytes, histiocytes, Langerhans or Merckel cells, APUD cells
- intricate network of myelinated and unmyelinated nervous fibers among microblood vessels (arterioles, veins and lymphatics)
- radiating matrix into the epidermic basal layer indicating epidermic connections

This study was completed by an *electron microscope* investigation showing clear local endocrine and enzymatic activities particularly adrenaline secretion after electro-stimulation of the point. This original neuro-vascular interface was always found below the detected points with some variations particularly regarding those able to generate analgesia.

Finally after these physical and histological arguments, it is possible to accept the scientific demonstration of the real existence of the NVB (acupuncture point) even if the meridians, that the Chinese described with many details, doesn't exist anatomically. All attempts to use tracers like radioactive substances to prove their real existence were negative and finally they have to be considered as intellectual creations like the constellations in the sky which are lines joining stars or planets placed not on the same level and sometimes separated by light-years distance.

In order to get more arguments proving the possible functional action of NVB, a physiological experimental reproducible model was achieved using rabbit, which is an animal with symmetric locomotion of hind limbs. In fact generating a cutaneous pain signal on one side generates a double withdrawal reflex. That allows to have objective validation of a possible skin analgesia. After implantation of two needles within two NVB of a hind limb and electro-stimulation applied on the needles during twenty minutes, a real analgesia was observed. The animal is not paralyzed and can move on the ground. But the mechanical painful skin prick on the analgesic side doesn't create withdrawal reflexes, whereas on the other side a bilateral withdrawal was observed after painful stimulation. In addition, the delay between the beginning of stimulation and the analgesia strongly suggests a neurosecretion phenomenon. In order to validate this hypothesis, an injection of the serum obtained by blood centrifugation of an animal with analgesia was done to a naive animal. In a majority of the cases, it was possible to observe a real transfer of the skin analgesia almost in the same territory and a first biochemical screening indicated a possible role of an enkephalin. According to its regional action, it could be considered as a metameric antalgic neurotransmitter. Complementary investigations are in process to validate the result of this experimentation which can have interesting applications in the future for the regional treatment of pain disorders.

In addition, an *implantation of a microelectrode* after fixation of the rabbit head in a stereotactic frame was done within the parafascicular nucleus of the thalamus where the pain signals are projected. It was possible to demonstrate the suppression of the signals after stimulation of NVB and its persistence if the needles are placed few cm out of the points. This aspect obliged, for a good clinical efficiency of the acupuncture practice, to respect strictly this principle of action.

A problem remains which is to try to understand why such NVB exist in all vertebrates including men and what can be their functional role. Obviously it is not for a medical doctor to put a needle in and we formulated three hypothesis:

1. the *thermo regulation* is a complex but precise function which is very well controlled by reestablishing rapidly the normal body temperature for example after a muscular exercise. It is commonly accepted that an hypothalamic centre control thermo-genesis or thermolysis by reacting to the blood temperature feeding it. But it seems technically impossible to have only one thermostat for the thermoregulation of all the body

segments with some exposed parts to outside and others protected by dresses. That is why the NBV can play the role of peripheral thermostatic regulator able to modify the organ blood supply and particularly for the viscera which have as we saw a close functional connection with skin. Doing that they can modify the temperature in addition to the sweat glands secretion for thermolysis and the muscle shiver for thermo-genesis. Therefore modifying the blood supply of an organ means change its function and this process can explain a large part of the clinical efficiency of acupuncture on reversible functional disorders.

2. the NVB are located within the skin and it is normal to consider that they play an important role in the *maintenance* of it as neuro-vascular interface. As we will see later, the cell mobilization in relation with a cutaneous injury requires peripheral control units which can be those NVB. It was demonstrated as a clinical argument the efficiency of acupuncture needling around a bed sore to close the wound. In addition the connection between NVB and Merkel cells which are responsible for acquired immunity could be integrated in this skin maintenance.
3. even if the meridians have to be interpreted as virtual lines joining NVB, the unmyelinated fibers identified in are sympathetic fibers with predominant action on arterial diameter and in fact on blood flow as well as C fibers for pain transmission. The dermalgic reflexes of Jarricot described previously with their hyperalgic zones are clearly related to NVB. All the NVB are finally conveying different signals to spinal cord, reticular formation, thalamus and hypothalamus, representing a large network responsible for the management of what we call *homeostasy*. It can be defined as a state which is a maintained and regulated equilibrium of basic biological parameters controlled by the vegetative nervous system bipolar action and supervised by the hypothalamus closely connected with the hypophysis gland, representing the conductor of the endocrine orchestra. Therefore the functional entity of the whole body has to be understood as a very large, complex and intelligent neuro-vascular interacting system, fluctuating by time but conserving a form of homeostasic stability.

6. The regenerative skin: The healing process

That represents one of the most innovative biological auto protection of the body. Any form of rupture of the epidermic continuity generates a cascade of repairing coordinated events with a common finality to close the wound. The actors of this precise orchestration are local and migrating cells, growth factors and enzymes. The most frequent sequence of phases is as follows:

1. *hemostasis*: a tissue injury is commonly followed by bleeding. That induces the coagulation process with thrombocytes clumping, vasoconstriction in relation with vasoactive amines like histamine and serotonine, clotted blood after cleaving fibrinogen into fibrin and finally scab by dehydration.

2. *inflammation*: PMN (polymorphonuclear leukocytes) extruded from vessels are invading the wound in order to cleanse it and chemotactic agents are released like FGF (fibroblastic growth factor), TGF (transforming growth factor) and PDGF (platelet-derived growth factor). In addition, monocytes are exuding from vessels and become active macrophages which perform also this mandatory cleaning procedure using phagocytosis helped by their own secretion of TGF, cytokines, IL-1 (interleukin-1), TNF (tumor necrosis factor) and PDGF. This complex process of cell mobilization is going on few days and is characterized by some classical symptoms: rubor, tumor, dolor and calor. These symptoms are normally disappearing in few days if only the normal bacterial cutaneous environment is not modified by pathogenic germs introduced into the wound. But also in this case, the immunological defense can react positively or with a specific additional help by medical or surgical therapy.
3. *granulation:* four different and complementary events are occurring. First *fibroplasia* is the migration of fibroblasts into the wound in order to produce a new extracellular matrix necessary to support a cell ingrowth. Collagen fibrils are produced by a complex process starting by the precursor called tropocollagen cleaved by peptidases to give all form of collagen types I and III. Second the deposition of a *new provisional matrix* is performed and gradually replaced by a collagenous matrix, suffused with many fibroblastic components like fibronectin, hyaluronic acid, chondroitin sulfate and proteoglycans. Third an *angiogenesis* is needed to create a *granulation tissue* and is induced by a great quantity of growth factors like vascular endothelial, transforming factor β, angiogenin, angiotropin... Plasmin and collagenase are digesting basement membranes allowing migration, mitosis and maturation of endothelial cells able to create new blood vessels. This new vasculature is also stimulated by hypoxia following the injury and elevated lactic acid. Four is a *re-epithelization* by migrating epidermal cells from periphery using cytoplasmic actin filaments and dissolution of intercellular desmosomes separating epidermal and dermal cells. In this complex cellular movement at the growth speed in the order of 0,2 mm/day, the expression capacity of integrin receptors of epidermal cell membrane is interacting with a large variety of extracellular matrix proteins allowing to dissect the wound by isolating eschar from viable tissue and to bridge it.
4. the ultimate phase which can take few weeks or more is the *remodeling*. The migrated epidermal cells reorganize their basement-membrane proteins restoring their normal phenotype and reestablishing dermis attachment. A specific wound contraction occurs in relation with a very sophisticated phenomenon well described by J.W Madden in 1973 who identified a particular fibroblast phenotype called myofibroblast. It is made by large bundles of actin microfilaments placed along the cytoplasmic part of the plasma membrane with cell to cell and cell to matrix linkages in relation with complex growth factor interaction. Therefore these myofibroblasts have some similarities with contractile smooth muscle cells.

Finally the ultimate scar resulting from the described repair sequence has no more than 75% of the tensile strength of the replaced skin. In addition this normal procedure can be altered by abnormal factors like excess of collagen production which can generate hypertrophic scars and keloids or infections by pathogenic germs. In fact normally the skin has a great quantity of commensal resident germs living in a good intelligence with their living environment. When a wound occurs, a normal proliferation of germs Gram+ appears which can be replaced by germs Gram- and faecal germs which are integrated within the bacteriocycle needed for the cleaning phase of the wound healing. But real pathogenic germs can invade the wound generating abscess or necrotic tissue requiring an appropriate treatment eventually but not always by antibiotics or surgical approach.

This incomplete but consistent description of this regenerative skin function can clearly demonstrate the unsuspected complicated but intelligent organization of the skin, which cannot be, without a great difficulty, explained by random processes.

All these skin neural interfaces have been described in their normal state, but like all the organs of the body the skin have some changes in relation with age. We call this progressive degradation of structures by time: *ANATOCHRONESIS*. Skin aging relates to genetic, hormonal, metabolic and environmental factors. The epidermic cells are permanently reproducing and some age related DNA deterioration can generate a replicative senescence by shortening of telomeres forming the caps at the end of DNA strands. The consequence is that the epidermis is becoming thinner and more vulnerable. Regarding hormonal influence, the sex hormones are decreasing with aging and particularly for women during menopause the estrogen binding to receptors in skin are modifying the thickness, wrinkling and moisture of the skin. As demonstrated scientifically, the velocity of blood flow in capillaries is significantly reduced. The metabolic factors are playing a great role as well. The free radicals which are highly volatile molecules are participating to the oxidative stress, breaking down collagen, damaging DNA, releasing abnormally cytokines and participating actively to allergic reactions. An elevated blood sugar can also increase cutaneous anatochronesis by the process called *glycation*, in which sugars attach themselves to the amino groups of tissue proteins and particularly collagen creating AGEs (advanced glycation end products) which are very destructive for collagen fibers, losing elasticity and becoming rigid. A *matrix degrading state* progressively appears due to collagen degrading enzymes called MMPs (metalloproteinase's). That gives the particular aspect of aging skin. Moreover the gravity force acts on round organs like breast and buttocks often out of the plastic surgery possibilities. Wrinkles and fine lines in face deforming eye lids and mouth lips is a real depression motivation for elderly but a spectacular financial success for cosmetic industry. More dangerous are the deep perturbations of capillary circulation which explain, as we saw before, some structural changes in Pacinian corpuscles of the plantar sole justifying the important balance disorders in diabetic patients. The Langerhans cells responsible in the skin for the acquired immune defense can also be altered increasing the sensibility to infections. Finally the most dangerous environmental factor is the sun exposure producing long wave UV-A (ultraviolet radiations) and mid wave UV-B inducing oxidative stress and hyper pigmentation by melanin production representing the photoaging. The so appreciated tanned skin which becomes a must for a part of our society is in reality a real skin damage that it is also possible to observe on rural workers not for the same reason. Even if the sun exposure can be benefit for the vitamin D synthesis the real difficulty to apply the right radiation dose will push to prefer oral daily well controlled ingestion. In addition, tobacco use is damaging seriously the skin creating the typical smokers skin. The final consequence of this inevitable anatochronesis is that aging is never a progress nor a good motive for happiness.

7. Conclusion

Even if for didactic reasons the five aspects of the skin neural interface were presented separately, it is important to consider that they are functioning all together with many complementary links. That gives to the organ skin a great importance in the whole system. In fact skin is the largest organ of the body which is more than a barrier with outside world having enough mechanical resistance to support heavy stress and constraint. But also it has a very rich nervous equipment able to answer properly to the mandatory communication with the external environment as well as internal complex biological machinery. Therefore all medical actions for diagnosis and treatment are always done through the skin which has also a real anatomical continuity with mucosa of digestive, respiratory and sexual tracts. The abundant literature on it is with the diversity of research programs in progress all along the world the best prove for its major interest.

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