The new method for transdermic molecular transportation

1. Presentation
This is a new methodology which allows molecular transportation across the dermic barrier, permitting the introduction\of active agents at different depths into living tissues, in particular into the human
body.

It is therefore a sort of virtual syringe where instead of a needle there are pulsated and modulated currents based on a new concept in wave forms. The particular wave form used together with the gel formulation allow the active agents to penetrate into the tissues from 0.5 up to 10 cm approx. This is a greater depth than that which can normally be obtained with the current electrophoresis or cryoelectric methods (just a few mms). Thanks to this new technology higher local concentrations of the active agents used can be reached. Introduction tests of the active agents have been carried out using this method on New Zealand rabbits of about 2 kg. The results show that the concentrations of the products remain low in the blood, urine and faeces whilst they are high in the treated areas.

2. Relative Studies
Hydroelectrophoresis is a technique which uses an electric current in order to make active agents in aqueous solution penetrate inside the tissues. The electrophysiological, physical, chemical and biological influences of currents on tissues have been well known since the beginning of the century. These aspects are extremely complex because they re late to modifications of the cellular metabolism and the distribution of the electrical charges on the surface of the cellular membranes. When speaking of continuous and low frequency currents, we must consider their penetration and diffusion at the skin level and other tissues. The cutaneous layer and in particular the corneal stratum covered with a fatty film, give remarkable resistance to the passage of the current. In order to penetrate, the current must therefore make use of other routes, such as: orifices in the excretory ducts of sweat glands and sebaceous glands and possible scratches or excoriations. As far as other biological tissues are concerned, they can be compared 10 a series of salt water lakes, containing electrolytes in differing solutions, separated by thin protoplasmic walls.

The resistance given to the passage of the current is:
- Practically nil for electric solutions and
- Very weak for the cellular membranes.
In brief, the impedance of the cutaneous covering has a very high value compared to that of the other biological tissues. (Delherm).

3. Electrolytic physico-chemical properties
A state of ionization is present in all the aqueous solutions of substances which can be ionized.

Each molecule is dissociated in two ions:
- One, charged with negative electricity because it has an excess of free electrons carrying negative charges;
- The other charged with positive electricity through lack of one or more electrons.

The biological tissues are not exempt from this rule: the sodium chloride, present in high quantities, is found in the form of sodium ions, positively electrified (NA+). If the polarised current crosses a solution of this type, especially
biological tissues, a migration of ions takes place:
- One, charged with negative electricity because it has an excess of free electrons carrying negative charges;
- The other charged with positive electricity through the lack of one or more electrons.

If the polarised current crosses a solution of this type, especially

Biological tissues, a migration of ions takes place, more precisely:
- Those that are negatively charged, such as the Cl- ions, are attracted by the positive electrode;
- Those that are positively charged, such as the NA+ ions, migrate towards the negative electrode.

Inside the tissues the cellular membranes (muscular, nervous etc.) are polarised, in that they carry on the one or the other side electrical charges, positive and negative respectively:
- The majority of positive charges are found on the convex, external face of the cellular membrane;
- The negative charges are distributed principally on the concave, internal face.

At the moment of their migration, the ions are slowed down by the membranes which disturbs their initial state of polarisation. Therefore new differences of potential are created which:
- Generate counter-electromotive forces; -Modify the resistance of the different tissues;
- Oppose the passage of the current.

When the ions make contact with the electrode, they transform into free atoms through the loss of their electrical charge. In turn these atoms are combined with the water.
In short, a current is diffused inside the biological tissues by electrolysis, that is, movement of ions (and not electrons) for as long as there are ions available in the solution.
Having spoken about the physico-chemical and electrolytic properties, let us focus out attention on the intrinsic properties of currents and speak about transdermic transportation by means of hydroelectrophoresis varying the temperature.
The use of transdermic systems allows the area of clinical interest to be reached with concentrations of active agents higher than their limit of activity in a selective way and at the desired depth.
However the systems current1y used have limitations of low efficiency in permitting a sufficient transfer of substances and in the permanence times at the desired levels. However the use of hydroelectrophoresis at low temperature, a technological innovation compared to the current transdermic systems, increases the penetration capacity of the molecules to the desired levels based on theoretical physico-chemical parameters.

4. Applications
Hydroelectrophoresis (experimented at a university level) is a new method for conveying active agents which exploits the known principles of electrophoresis for the introduction of substances through the cutaneous layers, in the form of molecules, but which, different1y from ionophoresis, uses pulsated currents. An appliance specially designed for this purpose has been designed and built in Italy.
This appliance and the overall method are currently covered by a patent in all of Europe (B. C. E.), with priority transcription (P C T) in the whole world.
Hydroelectrophoresis at last allows us to overcome the barrier presented by the derma, avoid the premature dispersion of the drug into the blood, and create through the tissues interposed between the positive electrode and the target tissues a directional flow of ionized molecules, until reaching the relative tissues, whose cells have been metabolised.
Very favourable results have already been obtained in the treatment of acute and chronic inflammatory diseases of an orthopaedic or rheumatic nature (osteo-articular traumas, neuro muscular traumas, phlogistic articular processes, muscle or tendon sprains, acute and chronic arthritic processes).

One of the applications of hydroelectrophoresis current1y widely used is that in the field of beauty treatments; the use, that is, of this technique for obtaining a reduction in the accumulation of fat which precedes the tissue degeneration which leads to a connective organisation responsible for the bridling of adipocytes which renders the possibility of reversion of the cells extremely difficult and which is of such importance for women's beauty. The results obtained so far have been very satisfying.
Another application of hydroelectrophoresis is for the relief of numerous specific ailments relating to sports medicine such as localised inflammations caused by pulling muscles, dislocations, sprains, contusions, etc.
In general, Hydroelectrophoresis has so far proved particularly effective in the treatment of pain, in which the systemic drugs used (anti-inflammatory drugs and pain-killers in general) have strong side effects for different organs, in particular the stomach and intestine.

The research has been conducted, under medical supervision, over the course of about 5 years, on a wide range of cases including various pathologies of an orthopaedic and rheumatic nature (scapulo-humeral periarthritis, discopathy with lumbar sciatic neuralgia, results of articular traumas to the knee and the ankle, carpal tunnel syndrome, epicondilitis), a very high number of range of muscle and tendon sprains, as well as certain pathologies in the urological and ear, nose and throat fields.
The duration of the single applications varies from 15 to 30 mins. depending on the quantity of active agents (and therefore the aqueous vehicle) which is considered necessary to use according to the characteristics and the localisation of the pathological area.

5. Cellulite
Cellulite, known by all women as an aesthetic problem, is in reality a disease of the subcutaneous connective tissue. This tissue is abundant with an intercellular substance called fundamental substance, secreted by the cells and interposed between them. In this substance there are collagen elastic fibres, proteins, mucopolysaccharides, fats, blood and lymph vessels. The connective tissue supports and separates the muscles, nerves and organs, regulates the discharge of the products of the metabolism and has an important part in the defence mechanisms of the organism An accumulation of waste products, caused by systemic metabolic, endocrine, vascular, etc. problems, provokes an alteration in the connective tissue: cellulite, in which the fibrous tissue which imprisons the adipocytes gradually increases; the elastic fibres are reduced, the blood vessels become congested and blocked, the nervous fibres are squashed and begin to emit pain signals. To cure cellulite effectively, it is necessary, therefore, to act both locally and to eliminate the systemic causes.
As far as the latter are concerned, often a normal calorie level diet, the elimination of smoke and alcohol together with moderate physical exercise is sufficient; when there are also medical problems (venous stasis, obesity, hormonal alterations, etc.) the systemic causes must be evaluated and treated by a doctor.
Hydroelectrophoresis (hydro = water solution, electrophoresis = transportation by means of electric current) makes it possible for water soluble and ionizable substances to penetrate under the skin by means of the passage of an electric current. The innovation with respect to ionophoresis lies in being able to choose the depth from 0.1 cms to 10,0 cms to which the substance penetrates, and in the high percentage of compound that reaches the desired area (70/80% against 5%).
Hydroelectrophoresis is painless, does not have systemic effects and the results are evident right from the first sitting. Substances are conveyed which dissolve the fats and reduce the volume of the adipocytes.
Hydroelectrophoresis can be used in ali areas affected by cellulite, it does not leave marks, it is not painful and as it is only a local treatment without any side effects it can be carried out in complete safety.

6. Stretch Marks
Stretch marks or, more precisely, stria, are alterations in the skin which form part of the group of skin atrophies. They have an elongated, straight or wavy shape with distinct edges and a raised or depressed surface with a colour that varies from red/purple in the first phase to white in the second phase to a shiny pearly colour on the third phase; they can be up to a few centimetres long and between three and ten millimetres wide.

Normally stretch marks are not painful even though sometimes at their onset a pulling sensation and slight itchiness can be felt. They appear at any age and are localised on the abdomen, breasts, thighs, hips and buttocks; they appear in multiple parallel marks and remain, when not treated, for life.

Histologically, it is known that the stria atrophica results from a thinning of the epidermis caused by the atrophy oath layers of collagcn in the derma, linked with a reduction of the elastic fibres which are retracted and thinned at the edges of the stretch mark; this atrophied zone is not vascularised.

The cause is often linked to the sudden or progressive mechanical stretching of the skin, but other concomitant factors of endocrine origin seem to have an encouraging effect.
Numerous therapies have been proposed without however giving a real result for improving or solving definitively the problem of stretch marks which, although benign lesions, have significant importance in that they are a very common aesthetic problem in women.

Hydroelectrophoresis can be used in all areas affected by stria atrophica, it does not leave marks, it is not painful and, as it is only a local treatment without side effects, it can be carried out in complete safety.

7. Acne
Acne is a disease which manifests itself prevalently in adolescents, but particularly in the female sex; it can appear after puberty and in the twenties and thirties.

The primary lesion appears to be caused by an excessive production of keratin at the outlet of the pilo-sebaceous pore which prevents the sebum from being expelled with the consequent formation of a comedo (blackhead).
This comedo is called -open- as opposed to the -closed- comedo which does not reach the cutaneous surface to be expelled.

In this case the sebaceous gland continues to produce sebum, it swells and breaks open intradermically.

The sebum which has thus been freed in the derma acts as an irritant and then stimulates an inflammatory reaction with erythemas, pus and subsequent healing by fibrosis with the formation of scars.
Acne is normally found on the face, chest, back, shoulders and sometimes neck.

Despite being, in the majority of cases, a benign disease which heals spontaneously, the affected parts (face) and the age of the patients (adolescents) have led to research for numerous cures.

Today it is possible to treat acne effectively with a new painless technique with no side effects: Hydroelectrophoresis.

8. Pain Therapy
Hydroelectrophoresis has proved very effective, using common painkilling drugs (Fans) and antiedemigens, which in this method are used in a selective manner locally, focussing on just the region affected by the pathology. With this therapeutic treatment,

the healing process has a reasoned logic in that at the first analysis an analgesic action can be
effected (symptomatic treatment of pain) immediately after, in the same sitting, a restructuring action (healing therapy of the relative area).
The pathologies treated concern the whole panorama of acute and chronic traumatic diseases, amongst which osteo-articular and rheumatic diseases, neuro-muscular diseases and degenerative, articular and tendon diseases. In particular the pathologies carpal tunnel syndrome, epicondilitis, muscular contusions, loss of tissue substance and traumatic oedemas.

9. Literature

M. Misefari* M. Sartori

STUDY OF TRANSDERMIC TRANSPORTATION
OF DRUGS BY MEANS OF HYDROELECTROPHORESIS

Introduction
The systemic administration of drugs often causes unwanted side effects and in many cases it is impossible to concentrate the active agents in the area of clinical interest.
Numerous methods and instruments have been used up until now to concentrate the active agent locally, amongst which ionophoresis which gives the possibility of conveying substances which can be ionized into the tissues using a flow of current as a carrier.
However, amongst the various defects of the ionophoresis method, the most important is that represented by the low efficiency in transdermic transportation and by the distribution of the active agent almost exclusively in the superficial areas of the tissue.

A technical improvement on ionophoresis has recently been proposed (1): this uses a frozen solution of the active agent (cryoelectrophoresis) which however has the disadvantage of a significant superficial dispersion of the drug during the treatment owing to the Juale effect, thus permitting a maximum transportation of only 5% of the active agent.

It is true that cryoelectrophoresis does not bring about the introduction ofthe drug into the bloodstreams (2), but this is due exclusively to the vasoconstriction at the points of contact between the frozen solution and the skin, and that in the physical state of the solution (solid) the electrophoresis mobility is nil.
To solve these problems, an instrument has been used in which the conveyor is an Idrossimetilcellulosa (gel), in which the active agent is dispersed together with a electrophoresis mobility enhancer (SMA), which has the purpose of supplying an ionic strength appropriate for the type of active agent to be transported.
The method used in this study has been called Hydroelectrophoresis and it uses a computerised instrument which provides electric waves of variable form and frequency depending on the depth to which the active agents has to penetrate.
The goal of the following work is to demonstrate that most of the active agent reaches the depth pre-set by the instrument and at concentrations close to those of the active agent in the gel.

Materials and methods
Progesterone solutions marked with I 125 (Byk) 3800 cpm were used. The radioactivity was measured with the automatic instrument SR 300 (Byk). The treatment was carried out on adult New Zealand rabbits of an average weight of 1.980 kg with the pubic area and thorax shaved.
The taking of urine samples was carried out using a syringe under ultrasound. The taking of blood samples was carried out from the auricular vein.
18 rabbits were used subdivided into four groups of which the first three were made up of four rabbits each which were treated by means of hydroelectrophoresis with marked progesterone.
The third group was made up of three subgroups of two rabbits and was treated using cryoelectrophoresis with marked progesterone.
On all the groups the skin readings were taken at 3 cm from the cutis and at 6 cm from the cutis.

The tissues were homogenised and solubilized in 2.5 mi of NaOh 1 N and measurement of radioactivity was carried out on the solutions.
After treatment with cryoelectrophoresis in the pubic area at 1000Hz the radioactivity measured in the urine was 5% of the total whilst with hydroelectrophoresis the radioactivity measured was 79.6%. The activity measured in the lung at 6 cm from the cutis and with a frequency of 500Hz was of 4.7% for ionophoresis and just 2% for cryoelectrophoresis.

Conclusions
The measure of radioactivity indicates that cryoelectrophoresis is completely ineffective in the transdermic transportation of the marked compound used.
This result can be explained by the complete lack of electrophoresis mobility for substances in a solid state and the small amount of radioactivity measured resulted from the melting of the solid in contact with the skin and its subsequent passage by ionophoresis.
Hydroelectrophoresis, using an agarose gel, improves the migration of the radioactive compound during the action of the electric field and the use of the SMA solution creates an ideal ionic strength for encouraging the transdermic passage of the marked progesterone. We can conclude that hydroelectrophoresis is indeed innovative in the transdermic transportation of drugs whether they can be ionized or not.

BIBLIOGRAPHY

1. M. Materia, A. Aloisi, G. Mangano, N. Longo: "Studio valutativo del trasporto transdermico di principi attivi ionizzabili mediante crioelettroforesi" Terapia Fisica e Riabilitazione 1997.
2. M. Misefari, M. Sartori: "Trasporto transdermico della diossina mediante Idroelettroforesi" coming into print.

* Toxicological Division of the Hospital Agency "Melacrino Bianchi Morelli" Reggio Calabria