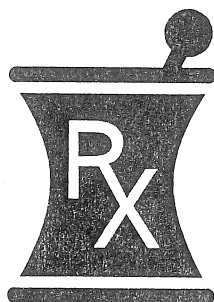


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**PLENARY LECTURES
THURSDAY, SEPTEMBER 7, 2000**

PLENARY LECTURE I.

(PT)

Calu-3: An in vitro model of the airway epithelium

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The airway epithelium is the site of action of a number of drugs applied by inhalation, and the target tissue for gene delivery in the therapy of cystic fibrosis. In vivo examination of mechanisms underlying drug transport or gene delivery at the airway epithelium are hampered by the inaccessibility and delicate structure of the lung. Inter-species differences in laboratory animals may render prediction of processes in human subjects difficult. Cell cultures offer the opportunity to model various absorptive epithelia under controlled conditions. Calu-3 is a human adenocarcinoma cell line, which features a number of properties common to the airway epithelium in vivo, such as tight intercellular junctions, cilia, and production of mucus. We have characterized Calu-3 cells in our laboratory, and evaluated them with regard to their use in drug transport and gene delivery studies.

PLENARY LECTURE II.
(BPK/PD)
Time Concept In Pharmacokinetics II

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Before talking about pharmacokinetic time, we should first have a look at time concept in general. There are many kinds of times as used in everyday life, like absolute time, biological time, physiological time, chronological time, subjective time, perceptual time, prime time, real time, psychological time, present time, physical time, etc.(1) At the beginning of this century, a very important time concept was put forth by Einstein: **Relative time**. We used to believe in living in a three dimensional world; whereas now, that concept was enlarged for the inclusion of time as the fourth dimension. After many years of discussion about this new concept, its physical meaning and significance has more or less been settled. We are now at the moment of extending this new and radical thinking into biological life processes. Biological relativity seems to rest on an individuals' perception of time. That makes it observer dependent. Bringing the subject down to pharmacokinetics, a simple example is as follows: Cefprozil half-life is 85 minutes in humans; 50 minutes in the dog; 18 minutes in the rat and 12 minutes in the mouse. And there seems to be no correlation across species. But if this half life is expressed in the number of heartbeats of the animal, it comes out to be 7250 beats. This fact is same in all the above mentioned mammals, i.e., same half-life (2).

The heartbeat time of mammals have been proposed with the following empirical relationship (3):

$$\text{Heartbeat time (sec)} = 0.2961 B^{0.28} \quad (1)$$

where B is the body weight in kg. Similarly (4),

$$\text{Breath time (sec)} = 1.169 B^{0.28} \quad (2)$$

To sum it up, any biological time can be expressed by (5)

$$\text{Biological time} = \text{constant} * B^{0.25} \quad (3)$$

It is observed that, body size is the prime role playing parameter. Body size on the other hand, is related to body volume through density. Volume is the main tri-dimensional property of matter; biological matter being a special form of matter. Now, if relativity says all matter is four dimensional and not three as was previously and erroneously supposed, it turns out that all biological objects, processes, kinetic behavior, etc. have an extra dimension that go along and has to be investigated.

The time that an individual perceives, is called psychological or subjective time. This time is more or less a function of metabolic processes within the body. The

administration of psychoactive drugs modify this perception and the user experiences all kinds of strange and bizarre observations.

The role of biological clocks comes to attention (6). The perception of time of the individual is variable. It is a recorded fact that, persons staying for days under the debris after a major earthquake, claim less time has passed during the unfortunate event.

The plasma concentration of a one compartment model drug given IV is defined by the following equation:

$$C = (D/Vd) e^{-kt} \quad (4)$$

where, D is the dose, Vd is the distribution volume, k the disposition rate constant and t, the time elapsed. From an allometric point of view, the clearance is defined as follows (1):

$$Cl = a B^x BW^z \quad (5)$$

and

$$Vd = b B^y \quad (6)$$

where, a, b, x, y, and z are empirical constants. B is the body weight and BW is the brain weight. Since,

$$k = Cl/Vd \quad (7)$$

Substituting Eq.s (5), (6) and (7) into (4) and rearranging gives

$$C/(D/B^y) = (1/b) \exp[-(a/b) (B^{x-y} BW^z)t] \quad (8)$$

A natural log plot of the left hand side vs. $(B^{x-y} BW^z)t$ yields a straight line with slope $-(a/b)$ and intercept $\ln(1/b)$. This plot is superimposable across mammalian species. The abscissa term has been named by Boxenbaum as **syndesichron** (7). It is a new kind of time based on body and brain weights. By using syndesichron as the time unit, single pharmacokinetic parameters are obtained for the whole mammalian species. Using similar arguments, Boxenbaum described further time scales under the names **dienetichrons**, **kallynichrons** and **apolysichrons** (8,9). They are all time units obtained by multiplying the chronological time by the body weight and/or brain weight raised to some empirical fractional power. This kind of approach opens up an entirely new understanding of biological processes, including drug action and pharmacokinetics (10). This field is now open for further interesting research. In fact, a recent report connects fourth dimension concept with fractal nature of networks in biological organisms (11).

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PLENARY LECTURE III.
(PDD)
Developments In Dermal Delivery

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Although the skin has attracted considerable scientific attention, it is surprising that the mechanism of percutaneous penetration has not yet been unequivocally identified. Advances in a number of biophysical techniques have provided considerable insight on the molecular interactions that occur when a drug passes through the stratum corneum. The most likely route is through the structured lipids of the intercellular channels and there are parallels between the determinants that control this process and the passive penetration across other membranes as diverse as CACO II cells and the blood brain barrier.

A simple evaluation of the most important physicochemical factors involved shows that partition, solubility and diffusion are of major significance. If any of these can be altered in a safe and rational way, strategies for enhanced permeation are possible. This is particularly important for skin permeation since bioavailability is often of the order of only a few percent. Chemical penetration enhancers such as the non-ionic surfactants affect diffusion parameters whereas simple solvents such as propylene glycol affect partitioning into the stratum corneum. If combinations of these two types of enhancers are used, synergistic effects are observed.

A further strategy is to increase the concentration of the drug applied above its solubility limit. This can be achieved using supersaturated solutions stabilized with anti-nucleant polymers. Although supersaturation is combined with chemical enhancement, synergism can be found.

It is possible to administer drugs that alter the biochemical composition of the skin lipids. These also modify the diffusional characteristics of the barrier. It will be interesting to see how these will develop into the next decades.

Physical techniques may also be used to promote penetration; these include the use of small electric currents (iontophoresis) ultrasound. Iontophoresis opens up a new pathways for penetration, the exact mechanism of action of ultrasound has yet to be determined. Iontophoresis can also be used in a reverse manner, extracting compounds from the blood supply. This can be used, for example, in the non-invasive monitoring of blood glucose levels. Other non-invasive techniques currently under investigation that provide estimation of drug levels in the skin include OptoThermal imaging (OTTER) and gradient field NMR.

The next years will see increased sophistication in the use of a variety of biophysical techniques that will allow us to probe and monitor the mechanisms of skin permeation at a molecular level.

PLENARY LECTURE IV.
(COS)
Advances In New Cosmetic Delivery Systems And Active
Ingredients

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New delivery systems and controlled release technology are expanding the cosmetics industry into areas previously known only to pharmaceuticals. Consumers today are much more informed than in the past in the areas of skin care and aging due to popular media covering these topics as well as advertisements by cosmetics companies. They no longer stick with a product simply because it smells good and makes them feel pretty when they apply it. As a result, consumers expect and demand real performance and benefits from their products.

Since the advance of alpha hydroxy acids (AHA), vitamins and ceramides, cosmetics have taken entirely new role as they have become cures for specific skincare illnesses and many formulation opportunities arise. They are anti-aging, anti-acne, oil-controlling, free-radical scavenging, sunscreen containing miracles in a cosmetics product package.

A new trend in the search for healthy, vibrant skin is the idea of barrier repair. The skin is the body's largest organ and its primary function is to protect the body by controlling what comes in and out. Due to instability, irritation to skin and difficulties in incorporation of these new ingredients into a cosmetic product, it becomes necessary to incorporate active ingredients first into a delivery vehicle in order to formulate a stable, effective product which produces perceivable benefits.

The objective of most controlled release delivery vehicles is to provide continuous benefits of active ingredients while stabilizing those ingredients and maintaining the final product's aesthetics. Delivery systems could be designed in many shapes and sizes. They range from traditional liposomes and natural materials to synthetic structures designed for controlled release. Among these, niosomes, transfersomes, glycospheres, multiple emulsions, microemulsions, microsponges and liquid crystals could be counted. Benefits of controlled release technology are often dependent not only on active ingredients but also upon the delivery system itself.

Sources of new active ingredients could be natural, bio-technologic, semi-synthetic or synthetic. These substances function as replacing natural elements of the skin (e.g. natural moisturizing factor), stimulating the biological functions, protectors of skin especially from UV rays, slimming and healing agents.

PLENARY LECTURE V.
(CADD)

Calculational Models For The Prediction Of Peroral Drug Absorption

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Drug permeation through membranes is an important issue in modern drug development. Most recently, various theoretical methods for the prediction of gastrointestinal uptake by passive diffusion have been established. They are supposed to support pharmacokinetic in vivo investigations, to save in vitro or animal studies, and to extend knowledge about the drug properties in general. The new calculational methods can be sub-divided into fragmental approaches, molecular modeling techniques, and combinatorial analysis. In various studies, it has been demonstrated that the octanol/water coefficient $\log P$ fails in the prediction of gastrointestinal drug absorption. Even simple counting of hydrogen bond donor and acceptor sites within the molecule has been found to be superior. Hansen's three dimensional solubility parameters weighten the hydrogen bonding capacity of a molecule and are therefore supposed to supply more precise information. Hence, pharmacokinetic properties of drug substances with diverse molecular structures can be estimated quickly. Advanced molecular modeling techniques including molecular mechanics, quantum mechanics, and molecular dynamics methods have been applied. However, the most promising of these methods, dynamic polar surface calculations and molecular dynamics of membrane structures, are still-time consuming and produce scattered results, too. In combinatorial analysis using neuronal networks or fuzzy logics, predictive equations have been developed based on various molecular descriptors. In all studies, the molecular ability of hydrogen bond formation and the molecular volume appear as the most important factors. Substances with a high hydrogen bonding capacity or large molecular size show minor absorption durations, low bioavailability, and a reduced number of absorption sites. The development of a suitable algorithm based on experimentally obtained three-dimensional solubility parameters, including conformational and constitutional aspects by molecular modeling calculations, seems to be a very promising task for the future.