Discurso de investidura como Doctor "Honoris Causa" del Excmo. Sr. D. Raphael Mechoulam

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The importance of being a sceptic.

Excelentísimo Sr. Rector, Autoridades Universitas, Profesores, senoras y senores.

I want to thank you for bestowing on me the great honor of becoming an honorary doctor of your ancient University. When this University was established my family still lived in Spain. Then it went to Venice, where a Mechoulam was head of the famous Ghetto, then to Germany, Bulgaria and finally to Israel. And yet for 500 years, 15th century Spanish –mixed with many words of Hebrew and Turkish, and called now Espaniol - remained the family language. As a young child I spoke Espaniol with my grandparents. I feel today as if I am closing a circle.

A few months ago a dear friend of mine, Julius Axelrod, passed away. He was a great and a very original scientist. For many years he explored the biochemistry of neurotransmitters with outstanding success – for which he was awarded the Nobel Prize. The one lesson I learned from him was – 'It takes the same time to do original work, as to do routine work. Try for the new and unexplored '.

A second lesson I learned was from Elias Canetti – whose accomplishments were discussed here by Dr Guy Hermet in his Dr Honoris causa lecture in 2004. Elias Canetti was a fellow Bulgarian Jew, who was a major figure in European culture during the last century. A central theme of his literary work was the pernicious effect of crowds on reason and human development. While he addressed political and social themes, I believe that to certain extent his ideas may be relevant to scientific endevours. Don't we, research scientists, sometimes follow the 'group' rather than go for the unexplored?

But how do we recognize the 'new and unexplored'? One way is to look for deductions, fully accepted by present day scientific dogma and reexamine anew the basis of their acceptance, using now modern methods - be they

technical or conceptual. A sceptical mind is an excellent tool in this endeavour. In my presentation I will try to give a few examples from our work..

In the early 1960's when I started my work on the plant cannabinoids, the field was considered to be fully explored. There were hundreds of old papers in many languages and in the 1930's famous scientists had worked on Cannabis. Hence most scientists working on natural products assumed that nothing new –either in chemistry or in pharmacology - could be found there. But a careful, sceptical reading of the voluminous literature disclosed that, on the basis of modern criteria, the active constituent had actually never been isolated in pure form, its structure was not known and its pharmacology and biochemistry were based on work with mixtures. No granting agency was willing to support research on this topic. However when we isolated the main constituents of Cannabis - Δ9-tetrahydrocannabinol (THC), cannabidiol, cannabigerol and many others – the field became part of the main stream and thousands of publications appeared. But the biochemical basis of the action of the cannabinoids remained obscure for another 20 years. The reason was the acceptance of the dogma that the cannabinoids act on the lipids of membranes. This was based on experiments, which showed that the activity of cannabinoids was not stereospecific and therefore could not be associated with action on receptors and enzymes. A close examination of the existing data showed that actually they were not based on acceptable premises and a few, new experiments in our laboratory showed that the activity was in fact fully stereospecific, hence the activity could be due to action on specific biological molecules. Indeed shortly thereafter Allyn Howlett in St. Louis found that THC binds to a receptor. Receptors are not formed in order to bind plant molecules, but serve to initiate a cascade of reactions when activated by an endogenous constituent. A few groups, including ours, started a search for such a molecule. The transmitters, modulators, cytokines and related entities discovered today are usually proteins or peptides, hence most groups looked for a compound of this type. We were rather sceptical of this approach. THC is a very liposoluble molecule, hence we assumed that we should look for an endogenous molecule with the same physicochemical properties. Such an investigation requires different chemical techniques than that for proteins. Indeed the 2 endogenous molecules we discovered that bind to the cannabinoid receptors were very liposoluble. We named them anandamide – from the Sanscrit word for joy – and 2-arachidonoyl glycerol. These 2 endocannabinoids have been investigated by many groups and have been found to be involved in a long

list of physiological processes. These include neuroprotection, appetite and suckling, inflammation, reproduction, emotions, bone formation, to name just a few. In Spain there are numerous groups working on various aspects of the endocannabinoid system – from involvement of endocannabinoids in neurological diseases such as Parkinson's disease and Alzheimer's disease, as well as cancer and aspects of drug abuse, to more basic aspects such as memory.

Allow me to end with some more recent work initiated because of our scepticism of long accepted paradigms. Incense burning has been part of religious ceremonies for millennia. In ancient Egypt it signified a manifestation of the presence of the gods and a gratification to them. In ancient Judea and Israel incense burning was also a central ceremony in the Temple and only priests were allowed to perform it. In ancient Greece incense burning was both an oblation and a protection against demons. In Christendom its use in worship and religious processions has continued since the 4th or 5th century A.D. In all religions it symbolizes the ascent of the prayers of the faithful.

We assumed that the spiritual exaltation caused by incense burning, particularly on the conductors of the ceremony, who presumably inhale large amounts of smoke, would be enhanced by a putative, mild psychoactive effect caused by the constituents of incense. We found only vague indications in the ancient and medieval literature that incense may indeed cause effects, which today can be termed psychoactive. In the Old Testament it is stated that the smell of incense "makes the heart glad" and Herodotus mentions that "Whenever a man of Babylon has intercourse with his wife, he sits before an offering of incense, and the woman sits opposite him…".

The resin of *Boswellia* species, particularly of *Boswellia carteri* (Burseraceae), known as frankincense or olibanum (in Greek) or lebona (in Hebrew), is a major component of Middle Eastern and European incense, and apparently has been used in worship since ancient times, It was a major product of commerce - frankincense was grown in the southern part of Arabia and in East Africa and camel caravans brought it north to Egypt and the Middle East.
There are scattered indications that it may have sedative properties. In the Middle East during the first centuries A.D. it was administered in wine to prisoners sentenced to death, to ‘take away’ or to ‘confuse’ their minds . In

Abyssinia, where Boswellia trees are common, it is believed to have a tranquilizing effect and to "relieve people from evil spirits".
We found that incensole acetate, a component of Boswellia, is active in mice in a tetrad of assays commonly used to evaluate cannabinoid activity. These, and additional data in mice indicate that incensole acetate causes pharmacological activities reminiscent of those produced by THC and by anandamide, the endogenous cannabinoid, but its activity is somewhat lower. However, as it does not bind to the CB1 cannabinoid receptor, its activity is obviously not via this particular mechanism. On the basis of the content of active material in the resin and the level of activity, compared to THC, we assume that its effect on users would be considerably lower than that of marijuana or hashish.
The above data give support to our original contention, namely that incense, used in the Middle East and Europe, may have mild psychoactive properties, which during religious functions may augment the exaltation produced, particularly on the person performing the ceremony. This effect may possibly explain the popularity of incense burning over millennia.

Allow me to return to the starting point of my talk: as scientists, indeed as intellectuals, we should try to be always sceptical. Present day media is very powerful and very convincing. We should try to go to the basis of presentations and be convinced that the facts support the conclusions. This is true for every sphere of life and certainly for every scientific area.