



The CCIC Podcast

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This month: Prof. Raphael Mechoulam
Interview by Dr. Mark A. Ware

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Introduction

Hello and welcome to the CCIC Podcast. The CCIC Podcast is a series of in depth interviews with leading experts and opinion leaders in the world of medical cannabis and cannabinoids.

The CCIC Podcast is brought to you by CannTrust™, a Canadian licensed medical cannabis producer.

In this edition of the podcast we are delighted to welcome Prof. Raphael Mechoulam from the Hebrew University in Jerusalem, talking about how he got started in cannabis research:

"...and the administrative head said, "yes, yes, yes, he is reliable" so he said 'OK, let him come over', which I did, and took 5 kilos of hashish."

and areas of cannabis research that require further study:

"...there isn't a single clinical trial with cannabis in cancer. Not with THC, not with CBD, not with a defined mixture. That's a shame."

Professor Raphael Mechoulam is the Lionel Jacobson Professor of Medicinal Chemistry at the Hebrew University in Jerusalem, Israel.

We spoke on March 16th, 2015.

Dr Ware: Tell us about how you first became active in research with cannabis. Was there a single person or event that you can recall that started you going in this field?

Dr Mechoulam I started as an organic chemist, or a biochemist if you wish, interested in the chemistry of natural products, as well as the chemistry of related compound, and I was quite amazed actually at reading a review on cannabis in the 1930s, and I was quite surprised to find out that the active compound in cannabis had never been isolated in pure form and its structure was unknown. Now that's in complete contrast with morphine which had been isolated from opium 150 years previously, or cocaine which had be isolated 100 years previously from coca leaves, so it didn't sound, something was strange there, and some excellent people had worked on it. Well we know today that it was very

difficult to do that because the cannabinoids are a mixture, almost 100 cannabinoids are present in the cannabis plant, so with the techniques available, apparently they were unable to do that. But in early 60s, the techniques were better, so we decided to go ahead. There was something else, because of the laws in various countries, most academic people were unable, or thought they would be unable to do any work on cannabis, because they needed someone to look over their shoulders all the time. In a small country it was probably easier, so I just got through to the administrative head of my institute to come between the police, and I asked for hashish. The fellow on the other side just started saying, "is he reliable?" meaning am I reliable. The administrative head said, "yes, yes, yes, he is reliable" so he said "OK let him come over", which I did, and took 5 kilos of hashish. I didn't have a car at that time, so I went on the bus, and people on it were looking around wondering about the smell. Nobody realized that I was carrying 5 kilos of hashish, and that's how it started.

Dr Ware That's a great story. In the time since you isolated THC, and published your landmark study on the structure of THC, it's been 50 years since then, what do you consider to be some of the most significant scientific achievements that have taken place since that time?

Dr Mechoulam Well I believe that THC is of course a compound that is being used all the time by millions of people, but from a scientific point of view, the most interesting part is probably that this compound lead to the discovery of a new biological system. THC binds to very specific receptors in the brain or all over the body, and that's what causes these receptors to start a series of reactions. Now, we thought that there should be compounds in the brain or in the periphery that actually the body makes! That by chance, a part of the plant binds to the receptors. So we went ahead looking for these compounds, and we found two of them. Anandamide and 2AG, now these two compounds turned out to be of extreme importance, they seem to be involved in a huge number of biological reactions. As a matter of fact, two scientists at NIH, George Kunos and Lyle Craker_senior people at the National Institutes of Health in the U.S, just wrote a review, and they write in this review that the endocannabinoid system is involved in essentially all human diseases. Now that's a very strong statement, whether it's completely true or not, well one has to see, but they are certainly involved, so here we have a new biochemical system of extreme importance. So this is the major thing that has happened, THC is fine, it's present in the plant, but the discovery of a new biological system, which is involved in so many reactions, I think this is of major importance in biochemistry and pharmacology.

Dr Ware Switching from the science just for a moment, it is certainly not lost on you that with cannabis, there are many policy issues flying around and to this day they continue to be a challenge. As someone working on cannabis, you've had lots of opportunity I imagine to engage in policy making, or you've been invited to participate in policy making

around cannabis for medical purposes. Do you think there are still policy gaps that need to be addressed with respect to accessing cannabis for medicines?

Dr Mechoulam Well, I tried to separate two issues. The recreational cannabis, and the medical cannabis, they are two different things. Recreational cannabis as I see it, is a social issue. If in a country most of the population decides they want to have recreational cannabis completely free, well that's a political issue. The way most of the people say tobacco should be available, high alcohol (whiskey) should be available, maybe they would like recreational cannabis to be available also. I don't think so but that's something else. Medical cannabis is something completely different, we know the cannabinoid system, and therefore THC and other compounds found in cannabis are of extreme importance. For many years we have been trying to introduce pure cannabinoids as drugs. About 35 years ago we showed that cannabidiol, which is a component of cannabis which does not cause any side effects, it's not toxic, and it's an excellent drug for epilepsy. We published that and nothing happened, then a couple of years ago, parents discovered that children that have certain epileptic attacks, (and there are some very nasty epileptic diseases) they found that cannabidiol was the only compound that helped them. Now why we had to wait 35 years to give cannabidiol to these children is beyond me, but that's what happened. Now a lot of people are trying cannabis with a lot of cannabidiol, and giving it to children to help them. Actually, I think the children should be given pure cannabidiol, there is no reason why these children should be getting cannabidiol with any THC, they don't need THC, they just need pure cannabidiol. There are a lot of things that can be done; we tried quite recently a clinical trial in post-trauma patients. We gave them 5mg of THC in oil under the tongue, three times a day, and we had very positive results. These post-trauma patients were previously afraid to go to sleep, because they would recall in the middle of the night something that happened to them, and that's why they have the trauma. With cannabis they slept very well, and the psychiatrists went through all the trials that are known for post-trauma, and they were positive, so here we have something. The trial was done on only a few patients, as we didn't have the money or the background to do it on a larger scale, but here we showed that it could be done. So there are a lot of experiments that are going on, unfortunately not enough, but in schizophrenia, a German-American group found that cannabidiol, at very high doses, is an excellent drug against schizophrenia, and it doesn't cause any side-effects. The anti-schizophrenia drugs used today have side-effects, and many patients refuse to take them. So why not use cannabidiol? Maybe companies will try to find cannabidiol-based compounds, which are more active. This is something in medicinal chemistry that is very well known, people take a plant compound, which has activity, and they try to improve it. It can be done with both THC and cannabidiol. There are a lot of other things that can be done as well, so I'm not sure that we should go on, giving forever mixtures or extracts of cannabis, maybe we should be giving the pure compounds, as with many other drugs. If this happens, the chances are many more physicians will accept treatment with cannabinoids. Now, if we go back to what we are

doing here, Israel in this respect is one of the most liberal countries in medical cannabis, we have 20 thousand patients that get medical cannabis. Officially they have to get a permit with the ministry, there is an office there that does all that, but there are 20 thousand patients that get medical cannabis. For a small country of about 8 million, that's a lot of patients. And the ministry now is trying to have a list of all the diseases for which medical cannabis, whether it be cannabidiol or THC, is approved. Now there are three or four types of medical cannabis that are approved. You can get, a lot of cannabidiol with a little bit of THC, or you can get a lot of THC with a little bit of cannabidiol, or a 50/50 mixture. Well it depends on the disease, it depends on what the patient wants, but this is where we are going. I am a little bit involved in all this.

Dr Ware You mentioned that the pure compounds may be the future, and yet there is a lot of talk around the synergies between the compounds themselves and this entourage effect. Do you think there is still something that can be attained by having the right mixture of cannabinoids in an extract or in a pure form that could be superior to either of the compounds by themselves?

Dr Mechoulam Well we don't know, quite frankly I believe that there is something in the entourage idea we published. We actually coined the term "entourage" if you wish. Possibly for some diseases a mixture might be better, but unfortunately there are no clinical trials, we just don't know! I mean, its nice to say a mixture is better, but has anybody done that? The answer is no, we don't know and it is strange that we don't know because so many people use it. I believe that for anxiety maybe, cannabidiol is fine, but maybe cannabidiol with a bit of THC, (not doses high enough to cause undesirable effects of THC) may be better than pure cannabidiol. That is what I believe but there is no proof of that. The same may be true for depression. So one has to look forward, I mean, one has to get more clinical trials, and very few have been done, which is a shame.

Dr Ware You mentioned schizophrenia PTSD and epilepsy as diseases that require attention. What else do you think are the most important clinical or scientific priorities for the next few years for cannabinoid research?

Dr Mechoulam Well one thing being used already is a drug against nausea and vomiting, to cancer therapy. We tried that in children, there is a pediatric department here that takes care of children that are being treated for cancer, unfortunately children do get cancer much like adults, and it's quite a tragic situation. The children are vomiting, they have nausea and they are crying all the time, and the parents are in bad shape. We started giving them a couple of milligrams of THC under the tongue, and it was supposed to be a double blind study, but the physicians came to me and said: "No I can't do it. I know exactly who is getting it, because none of them that get it are having nausea, not a single one". So she continued doing it, she gave it four hundred times, and there was not a single case of a child vomiting or having any side effects from the small amount of THC that was given to them. It is outstanding for children, but I'm not sure it's being

given to all those children that have to undergo all the cancer treatments and chemotherapy. Of course the two biggest problems are pain and gastro-intestinal diseases, and I have no doubt that with certain types of pain, not all pain (acute), if you have a tooth to be taken out, cannabis is not the drug, but if there is pain due to some neurological problems, chances are that in many cases it helps. It is not 100% effective, the pain does not disappear, but patients claim they have less pain, or they do have pain but they don't care. So most of our 20 thousand patients get it for pain or for gastro-intestinal diseases. Cancer, here we have a problem, because there isn't a single clinical trial with cannabis in cancer. Not with THC, not with CBD, not with a defined mixture, and that's a shame. There is good evidence of cannabinoids against cancer, but we have to wait for the clinical trials. Its not enough that a patient comes and says that it helps them, because we don't have any, any strong evidence which will allow physicians to use these materials. Prostate cancer apparently can be treated with cannabinoids, it seems so, but there is no proof.

Dr Ware Israel has a long history of being active in this, in large part because of your involvement, and it's clear that Israel has a fairly liberal approach to using cannabis for medical purposes. What do you think makes Israel such a hotbed for cannabinoid research?

Dr Mechoulam Well one of the reasons probably is that at the beginning, there were a few chemists working with me on my group, so that we open the field to pharmacologists, and the pharmacologists open the field to bio-chemists and it went ahead with the clinicians, so we have quite a few clinicians that are aware. In most of the western countries, this did not happen, and if you look at Europe, very few physicians are willing to administer medical cannabis. In Israel we have a larger number of physicians who are doing it, so probably that's the answer. I mean going ahead on the logical way with chemistry, pharmacology, biochemistry and the clinic.

Dr Ware And where do you see cannabis research going in the next 50 years?

Dr Mechoulam Well first of all I sincerely hope there will be clinical trials. We have to do those trials; otherwise most physicians will not use cannabinoids, when they are trained to use drugs that have undergone clinical trials. If we don't have clinical trials, we won't have too many physicians doing that. On the scientific side, I believe there will be a lot of work on the endocannabinoids, and here something new is just popping up. It turns out that there are in our brain, and probably in our body, more than 200 compounds of the same type as the major cannabis compound formed by our brain anandamide. Anandamide scientifically is formed by fatty acids with amino acids. Well these are two types of compounds widely present in our bodies, there are about 200 compounds of this type, and it turns out, that those that have been investigated are of extreme importance. We found that one of these is an excellent compound against osteoporosis, so this is something the body makes against the disease. We found that a few other compounds

of the same type (cannabinoid-like compounds) fight the damage done by head trauma. We have compared this in mice of course, and we see that these compounds, when administered to the poor mice that had head trauma, have much less damage. So here we have probably a huge number of compounds that possibly act on a variety of diseases, and I believe that over the next decade, there will be a lot of work on these 200 compounds. And probably the main thing that will happen, is that pharmaceutical companies will take these compounds, will take THC, will take cannabidiol, will take some of the additional cannabinoid-like compounds, and make modifications in order to detain the medical aspects of these compounds, and lower the effects that we know exist. Chances are that we will have a lot of drugs based on the existing compounds. And I would like to mention a last thing, there are two types of receptors; one of them, when stimulated, causes the cannabis effect. The other one seems to be protective because it doesn't cause any side affects. Chances are the compound from this particular receptor is called the cannabinoid 2 receptor. Cannabinoids are all compounds, specifically in that receptor may become major drugs, because it is activating that particular receptor which is therapeutic. We have seen essentially no side affects.

Dr Ware In closing, this podcast will be listened to by people who are interested in cannabis and the science around cannabinoids. Do you have any final reflections or thoughts for the scientific community about what you think has been happening with cannabis and cannabinoids, just in a more general sense?

Dr Mechoulam Again I want to repeat, if there are clinical trials, physicians will accept them, as most of the patients rely on their physicians. Cannabinoids may become one of the major series of new drugs. Around 60-70 years ago people didn't realize for example that steroids are of importance. When they were discovered, the pharmaceutical companies were not particularly interested. Within ten years, they became a multibillion group of compounds of major importance. I believe that the cannabinoids are in the same stage today, and within 5 to 10 years I am sure we will have many cannabinoid drugs on the market for a variety of diseases, and I hope that this will happen.

Dr Ware Well Raphi you have been a leader in this area for many years, I thank you very much for taking the time this evening to talk with me. Congratulations on 50 years of tremendous service to the scientific community, and it has been a pleasure speaking with you today.

Dr Mechoulam Many, many thanks, and I want to express my gratitude to you and your colleagues for going ahead in what I believe is a very important field.

That was Professor Raphael Mechoulam, speaking to us via Skype from Jerusalem in Israel.

Thank you for joining us.

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