An Interview with Willem Scholten and Myra Klee: June 26, 2001

Ethan Russo

Russo: Firstly, for our readers, would you be able to tell us what the reason was for beginning this particular program.

Scholten: Well, actually, in other countries as in the Netherlands, many patients experienced that cannabis had beneficial effects on their disease. As it is now, prescribing and delivering cannabis as a medicine is prohibited. So, patients asked politicians, "Please, can we use cannabis as medicine?" We had some discussion on that, and our ministry then asked for the Health Council for an overview of the evidence for using cannabis as a medicine. The Health Council made an overview [of the literature] from 1970 to 1995, and concluded that there were many studies, but that almost all of them were case reports. Many did not state what was used in this particular case, so sometimes there wasn't even any mention whether it was cannabis or THC, and when they used cannabis, they didn't specify the THC content of it, or what was CBD. So, the advice of the Health Council and its advisory board to the government was that there should be more trials, and if done, it should be with clearly defined cannabis, or the purified substances out of the cannabis. Then our minister adopted that advice, and decided that there also should be a legal source for the cannabis. The Single Convention [of the United Nations] says then that there should be a government agency that acts as a regulator. So, it was the conclusion that we should form the Office of Medicinal Cannabis.

Russo: Very good.

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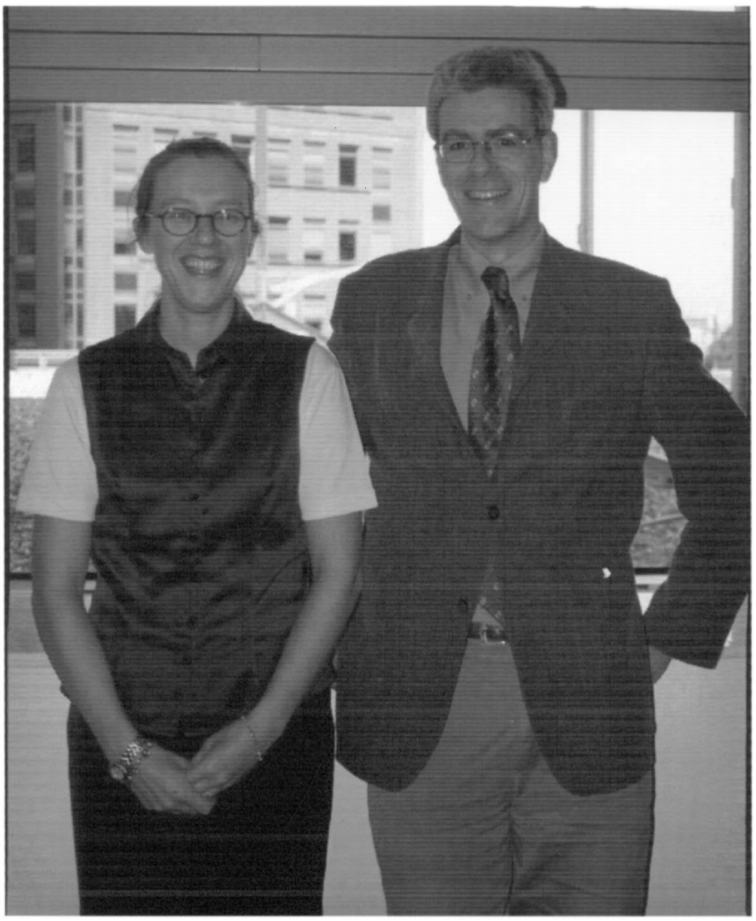

Scholten: Let me add the government decided to establish such an agency at the end of 1998. We made some preparatory work and it was formally established in March 2000. We started functioning as a government agency in sense of Article 28 of the Single Convention on the first of January of 2001.

Russo: I've heard previously that doctors in the Netherlands had less interest in pursuing use of cannabis with their patients. If that is the case, could you tell me why it is that they have been less interested than doctors in other European countries or in North America?

Scholten: Well, I'm not sure whether that is the case. I think in general, it is not confined to the Netherlands as a general tendency for doctors to be interested more in purified substances, chemical medicines, than in herbal medicines. Well, I always think that it's like the difference between opium and morphine tablets, which are accepted almost all over the world. In every country, morphine is accepted internationally, and cannabis is not.

Russo: So, in the Health Council's examination of the previous evidence, they did not look at information before 1970?

Scholten: Right.

Russo: So there was no examination of the extensive 19th century evidence in the literature. That was not taken into account?

Scholten: That's correct, but the older literature is not really the evidence we need for accepted medicines today. Of course, we know that cannabis was already mentioned in Chinese literature from 5000 years ago. But today, we require double blind cross-over placebo-controlled research in clinical trials. Prior to 1970, that wasn't done. Before I worked on cannabis, I worked on classical things and I've seen a lot of literature from before 1970 and even in the 70's that the methodology of performing clinical trials was very bad compared to today's standards. Well, often they were placebo controlled but without enough power to prove the efficacy, and so on. But, there is another aspect, and that's that the trials never had been done with standardized products, and that's true even for newer trials. That's still the problem.

Russo: Would it be fair to mention that those preparations were not available to any clinician?

Scholten: I think so. That brings me to the point that I can explain to you how our plan is to work, because this is exactly the problem. If you want to do a clinical trial you have to do that with a clearly defined preparation. The main thing is that it's clearly defined and that it's reproducible. So you have to prepare an assay of the main cannabinoids in the preparation and to make fingerprint of the rest. If you only required that, you could take seized cannabis from the police, but then you have a problem if you say in the end, "Well it worked fine," so that we can give it also to other patients. You have to conclude that the next cannabis that is seized by the police may have different properties. So, you have to start by growing the cannabis, and to use well defined breeds, to grow in well-defined circumstances. Then you have plans that you can reproduce every time. Then you make preparation according to pharmaceutical standards for use in GMP [Good Manufacturing Practice], and you test it with GCP [Good Clinical Practice], and so on. Then you can come to conclusions

that you have a preparation that works, and if you can register it, complying with the normal standards that are required for every drug.

Russo: In the Netherlands, are other herbal agents accepted as medicine?

Scholten: Some are. The problem is that, in many cases, the efficacy is not shown very well. And for other herbal preparations, the problem is that manufacturers say, "Well we cannot make enough profit for it." But, we think it's possible by using patented extraction methods by using registered plant breeds to protect the product that the manufacturer will profit commercially in the end.

Russo: So would that be the situation with, for example, *Ginkgo biloba* or St. John's wort?

Scholten: I think gingko is a very nice example. In the Netherlands we have an extract that is patented and that is registered at the same level as many chemical drugs.

Russo: What would you anticipate or is there an identified source now for cannabis that meets the criteria that you discussed?

Scholten: Oh, we hope so. I think Myra can explain a little bit.

Klee: We have had communication with several growers, and we will try to find a grower that is capable of growing standardized cannabis, and somebody who we can trust, then we'd like to offer a contract. Hopefully there could be two or three companies. Everybody has got their institute that can investigate seeds, so hopefully we will have one or two growers.

Russo: Would these be here in the Netherlands?

Klee: Yes.

Russo: I had read something on the Internet, and I would be the first to admit that it's not always a reliable source, but it implies that the first material had actually been sent from the U.K.?

Scholten: No. The articles in the newspapers about this were wrong. We had our first importation of cannabis plants, but they were imported for scientific purposes, and not meant for medical application.

Russo: It is fair to ask the source of that material?

Scholten: Well, it's a government agency. We act also for other parties, so I don't want to make any statement about the character of the plants. I hope that you can understand.

Russo: Surely. Once a source is identified, what would be the procedure for patients and their physicians to utilize the material? Would it only be used in clinical trials, initially?

Scholten: Yes initially, and after that I hope we can interest a pharmaceutical company in the development of a new medicinal product and have it registered, comparable to licensing in the United States. And, as soon as it is registered, it can be marketed through pharmacies. Then it can be a prescription drug like, for instance, morphine tablets.

Russo: If someone had material that was assayed and reproducible, and they had a clinical trial for a certain diagnosis, and it was successful, how long would you anticipate would be needed to allow actual prescription of the medicine?

Scholten: Well, we hope it will be done in several years, I think in 4 or 5 years. Although the product still has to be developed, it's not the same as with new chemical entities. Then we would have to do all the safety assessments. I think with cannabis-based medicine, it is already clear that cannabis is not a very dangerous substance. Of the fresh herb, you can eat your own weight, and only then would there be a risk of dying of intoxication. In the longer run, cannabis is not among the most dangerous substances. What has to be done by a manufacturer is to ensure that his preparation has comparable properties, and it's easier than starting from the beginning in showing that the substance is safe.

Russo: Is it your belief that different strains of cannabis are more effective than others for a certain condition?

Scholten: Yes, I think so. That's why we require that cannabis use is standardized. If all the strains acted the same, you wouldn't need to standardize.

Russo: Yes. Are there steps underway to actually encourage clinical research?

Scholten: Yes. (Aside to Ms. Klee in Dutch.)

Klee: We have meetings with pharmaceutical companies, as well as with growers. We try to encourage the pharmaceutical companies to develop medicine. This can cost a lot of money, so their first question is how you can profit from it. We hope we will have one or two pharmaceutical companies interested soon. There are some smaller trials at the Free University Hospital of Amsterdam. One was just recently finished. Then, hopefully in September [2001] will come follow-up. We provided a small subsidy for it, to then compare smoking with tablets.

Russo: What is the disease that they are studying?

Klee: Multiple sclerosis.

Scholten: There are four main targets. We will start with the most promising indications. We said multiple sclerosis is one of our targets, cachexia in AIDS and cancer, and nausea and vomiting in radiotherapy, and later we added chronic pain.

Russo: Would it be fair to say that everything in the program is set up to comply with the Single Convention as it currently is written?

Scholten: Yes, I think we have to comply with two things. One is the Single Convention and the other, higher pharmaceutical standards. I think both are very important because you will not succeed if you don't comply with those standards. You also need to convince other countries that this is important, and if you don't comply with international standards they will say what you did is amateuristic.

Russo: Why is it important that the Netherlands be able to show other countries that there is efficacy? Is this a philosophical belief, or just trying to share your expertise with other countries that are not as advanced in the process?

Scholten: Well, it's not necessary that we show other countries that it's efficacious. The Netherlands is a small country with a little more than 16 million people. So the Dutch market is large enough to develop a profitable medicine, except if you market at a huge price. [Laughs]. We hope that it will be affordable to everybody. Then you need to cooperate with other countries that share the same insights.

Russo: Do you feel that current international law has interfered with research on cannabis?

Scholten: Well, I think modern insights are not the same as when the Single Convention came into force. You see, the scheduling of cannabis in the Single Convention says that there isn't any medical application for it, that it is Schedule 1. Schedule 4 also says it's among the most dangerous drugs. I don't think that the international community would say the same thing if it had to be rescheduled today. On the other hand, we also need to have scientific evidence, so it makes it important that what we are doing is done in a methodologically good, acceptable way.

Russo: It seems that as compared to the USA, where HIV is one of the indications of greatest interest in clinical use of cannabis, there seems to be less inter-

est in Europe, perhaps because it isn't so prevalent. Are you aware of AIDS patients in this country using clinical cannabis?

Scholten: Oh yes, there are. We have an advisory committee to our office . . .

Klee: They will meet today. They come together every two months. We have subjects that are interested on the agenda, and there are representatives from the ministry, and also from several patients groups. They also have somebody from the multiple sclerosis group and one of the HIV patient groups.

Russo: Looking at another subject, it's my feeling that Americans receive some very biased information and half-truths about drug policy in the Netherlands. Is there any effort that your government is putting forward to try and make things clearer so that there are not these misconceptions?

Scholten: Let me first say that our office is part of the pharmaceutical affairs department and we have a separate addiction care department. I don't have clear detailed knowledge of the addiction care part of cannabis, but we make a lot of fact sheets and so on, and they are also available on the Internet.

Russo: Would you care to comment on General McCaffrey's visit to this country? Was there much fallout after that in terms of policy?

Scholten: Well, I don't think I should need to comment on McCaffrey's journey. Compared to other countries, our [drug usage] results are no worse than those in other countries. For instance, in the *British Journal of Psychiatry* [(MacCoun and Reuter 2001)], there was an article that compared different countries and the Netherlands was doing no worse than other countries.

Russo: Very good. Do you feel that cannabis tourism has been a problem and, if so, in what way?

Scholten: Well, it is not really an issue of medicinal cannabis, of course. I think it affects the use of medicinal cannabis in a sense that we want to separate medicinal cannabis and recreational use of cannabis. That's because we don't want to stigmatize patients as drug users. So, that's also why we placed our office in the Pharmaceutical Affairs Department and not the Addiction Care Department.

Russo: In that regard, do patients now currently go to coffee shops to get their cannabis?

Scholten: Yes, at the moment there is no special status for medicinal use of cannabis. So, you just buy cannabis and it's not marketed for recreational use

or for medical use. Everybody who wants to buy cannabis can go to coffee shops and use it in a medical way or in a recreational way. It is illegal.

Russo: But, they are limited, as anyone else would be, to 5 grams per purchase?

Scholten: Yes. Although the use of cannabis in the Netherlands and trade in it is prohibited, our prosecutors have a priority policy that they only want to prosecute bigger cases. Officially we have declared that under 5 grams, nobody will be prosecuted.

Russo: Following from that, what are the laws or the understandings about patients' ability to grow their own plants?

Klee: The same as for other people.

Russo: And those are?

Klee: Those are five plants maximum a person.

Russo: There is no limitation on how large they are or whether they are indoors or outdoors?

Scholten: No, people can be very creative by making their plants large. In practice, I don't think people will make very large plants. I think from a medical view there is another problem. It's not a legal problem. If you say people need standardized cannabis to treat their disease to know what they can expect, of course, they can have to some extent beneficial effect from their home grown plants too, but they will not be able to standardize to a very high degree. In the end, that can be a problem. For instance, if you're a patient with multiple sclerosis, and you use cannabis as medicine, you don't want to become high. You want the symptoms to be treated without becoming high, so then you can do your work. What I hope is that we are able to find breeds to make extracts from the cannabis plant that treat the patients without making them high. If they grow their own plants now they will grow breeds that make them high. So then, it is not the optimal therapy.

Russo: I would like to have your comment on how the illegality of cannabis has prevented its exploitation or use as a medicine that might be valuable to certain patients.

Scholten: I think it's difficult to do clinical trials if you need to be licensed first to have the substance available. In the past it was very difficult to get such a license, so this interfered with getting the evidence, but then it's just a circle.

Because there's no evidence, it is difficult to get the license. I think internationally we are in an era in which, in many countries, the governments are thinking about accepting just an objective clinical trial and assessment of the potency of cannabis as medicine. And if we have this, maybe the outcome can be negative or it can be positive, but then we have scientifically seen the value of it, and can then decide on that basis what to do in the future.

Russo: How has the policy of tolerance for cannabis helped lower crime rates?

Scholten: The Dutch policy recognizes a difference between hard drugs and soft drugs. Cannabis is a soft drug, one of the few. The others are hypnotics that are classified as soft drugs, and all the other drugs are hard. We have a policy of only tolerating soft drugs in coffee shops, but as soon as they sell hard drugs or alcohol, or sell to minors, the coffee shop will be closed, and also if they sell in too large amounts. So, we make a good separation in the cannabis markets and the hard drugs. This permits us to clearly see what's going on in the coffee shops. I think that has diminished crime and criminality in coffee shops, but of course it's always like a balloon. If you press here, it becomes wider another place. Every country has that problem; the criminality is in the hard drugs.

Klee: Although there is tolerance, Amsterdam is becoming more strict, in that they have reduced the number of coffee shops, especially within a certain area around schools. They said that for every coffee shop that's closing, nobody else is going to get a license for it. So, in the last year the number of coffee shops has been very much reduced.

Russo: This is a politically sensitive question, but has your office been criticized officially or unofficially by American agencies?

Scholten: Not as far as we know. To start, as an international agency we sent a letter to the United Nations to the INCB [International Narcotics Control Board] and we also sent it to many other countries via our embassies. We did not get any reaction from, for instance, the United States that it was not done in the proper way. On the contrary, formally we already had some contact with NIDA [National Institute on Drug Abuse] and they were somewhat positive about our plans, and I think they will accept what we are doing. I think it will do, at least as long as we comply with the requirements of the Single Convention.

Russo: Are there similar plans that you're aware of to do what you are doing in other countries in the European Union?

Klee: We see a lot of movements in other countries in Europe. In Spain, there are some regional parliaments that are trying to allow cannabis for patients. In Italy, something is going on, and in Germany is already there's a company who wants to do a trial. We are organizing an end of year conference and we would like to invite our colleagues from the different countries. We would like to express our view that it's important to do clinical trials that are randomized, double-blind. We hope that the other countries will also follow the way of the clinical trial with registration.

Scholten: The conference is meant for representatives of the other states, I think at maximum, at most thirty representatives.

Russo: In your program, for example, let's say that in the U.K. there is a clinical trial that is undertaken with a preparation that meets your specification, would you accept that result or must it be done in this country?

Scholten: The legislation on medicines is harmonized all over Europe, and as soon as one company has registration for a preparation at the Medicine Control Agency in London, it can be registered, in principal, all over the European Union within 3 months. This is called the Mutual Recognition Procedure. It is also possible that they apply at the European Medicine Evaluation Agency and then its registered all over Europe at one time.

Klee: It could be possible that this company is trying to register a medicine for multiple sclerosis, and may be at the same time a Dutch company is doing a trial with medicine for cachexia, for example.

Russo: Are you aware of any countries or programs in other countries, have they approached you about using their information? In other words, is there any movement that you're aware of by companies from other countries to introduce their medicines here?

Scholten: Marinol® is already on the special application basis. It's not licensed in Europe, at least not in the Netherlands, but if patients apply for it, it can be imported. I don't know of any other preparation that is marketed in Europe at the time.

Russo: Let's use as an example GW Pharmaceuticals. I understand that they have an Initial Public Offering now and they have trials underway in the U.K. If they have positive results, would you anticipate that they would approach you to use their preparation?

Scholten: Oh yes. It's no problem. If they register, it can be marketed in the Netherlands, too. Our philosophy is that drug development is always an inter-

national affair, an international concern. So it makes sense that if a Dutch company develops a product, it also has to do clinical trials in other countries, and GW needs to do clinical trials and needs our hospitals to find enough patients.

Russo: I believe in this article of yours [(Scholten 2000)], you mentioned that you might consider supplying cannabis for research in other countries, under existing law in the Single Convention. Is this really something you would anticipate doing? Under what conditions would you consider exporting cannabis or whatever kind of preparation that met these standards to a company or other countries for research?

Scholten: Well, the first condition is that the authorities of the other country give their consent. That's to comply with the international law. Furthermore, we need to be able to find growers for the amount they need. If they want a very large amount, we won't probably be able to produce it, but I don't think it will be a real barrier for cooperating with companies from other countries.

Russo: So, as it is written now, if a grower in the Netherlands wanted to take part in the program, and they had a standardized strain, agreed to sell all of the material to your agency and kept track of everything else, they would be able to do business and potentially supply to another country?

Scholten: In principle, they will able to do that. There is another condition and that's that we don't want any criminal involvement. So, every grower will be screened before we contract with them.

Russo: Is there any movement currently for Holland to withdraw from the Single Convention?

Scholten: No.

Russo: So that has not been discussed at all?

Scholten: No, no. Well, of course people sometimes suggest to the government to withdraw, but it's no real option, I think.

Russo: Is it true that medical patients get a discount in the coffee shops for their purchase of cannabis?

Klee: I read that somewhere that there are certain coffee shops that have this agreement.

Russo: Do you know what kind of documentation the patient needs to provide for that?

Scholten: I think it will be in writing from a physician to a coffee shop. It's not official, of course, because all of what those people are doing is illegal.

Russo: Is there any advice that you might be willing to provide to researchers in other countries as to how to initiate a program such as yours?

Scholten: Well, what I see as the main problem in the discussion on the use of medicinal cannabis is that they don't realize that research must be reproducible. So people often start at the wrong end, in my view. If you don't make a preparation that you can use again after doing a trial, you can only make a general statement as a conclusion, but you can't say that we will give the patient again the same material.

Russo: Can people get by that through the use of a cloned strain of cannabis?

Scholten: Well, if they specify enough, that could be a possibility, but the growing circumstances also influence the product and the extraction process. For instance, I heard of people making tea of cannabis using a little butter to enhance the solubility of the cannabis and cannabinoids. But, if patients do not know how much butter they add they make a different strength of the tea each time.

Russo: Are you encouraging any research on the use of vaporizers as an alternative to smoking cannabis?

Klee: Yes, of course. Smoking is not our first priority because it doesn't seem to be healthy, so, either a vaporizer or another medicine form. The trial that was done last spring showed that swallowing may not be the best solution, but a vaporizer could be. So it depends on the pharmaceutical company if they are able to develop the right dosage form. But, we realize that smoking is not the right way of taking medicine.

I also want to add something about your question from screening because we are, of course, not capable of screening growers for the things that they do in the future, but we are making a contract with them, and we are going to control this contract. Of course, we are able to stop the deal if something goes wrong, but we have tried to practice that way so we are screening before we give them a contract.

Russo: What is the level of interest among the growers out there in participating in your program?

Klee: I think the growers that we spoke with are mostly involved because they, or somebody in the family have a disease, and they became familiar with the

product. There is also an institute in a university. They have knowledge about it because they developed hemp breeds for rope.

Russo: Well I think that we went through the questions. Are there other comments that you would like to record?

Scholten: Well, I think we explained the way we are working and what the most important aspects are.

Russo: Thank you very much.

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