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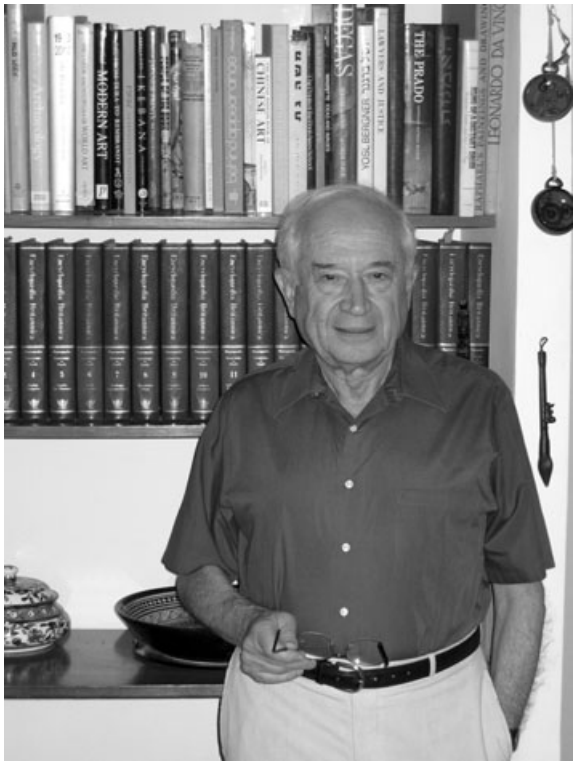
Conversation with Raphael Mechoulam



In this occasional series we record the views and personal experience of people who have specially contributed to the evolution of ideas in the Journal's field of interest. Entering what was, at the start, a neglected field, Raphael Mechoulam went on to pursue, over the next 40 years, a highly productive career in cannabis research. This interview charts a sequence of discoveries and reveals something of the dedication and intellectual daring which has characterized the enterprise throughout.

EARLY INFLUENCES

Addiction (A): Raphael, so often a person's later career has its roots in their childhood and the cultural atmosphere at home. Can you tell me something about your early life?

Raphael Mechoulam (RM): I was born in 1930—for my family a happy time in eastern Europe. The wounds of the First World War were not too painful any more and Hitler was still considered a demented curiosity. My father, who had graduated from one of the finest medical schools in Europe, in Vienna, was a prominent physician, head of a hospital, while my mother, who had studied in Berlin, enjoyed the life of a well-to-do Jewish family. Books, concerts, the theatre and medicine were part of my family background. I was sent to an American Grade School, where I had the only regular schooling I can remember. Then the Second World War broke out. Bulgaria joined hands with Germany. Anti-Semitic laws made our life almost unbearable. My father took a position as a physician in a village, with no running water or electricity, hoping that we would be more secure up in the Balkans. We had to move from village to village over the years. My father was sent to a concentration camp in Bulgaria, but luckily we all survived. In 1944 a communist regime was established. The new leaders, who had spent their formative years in Moscow, copied the Russian Soviet system to the last iota. I felt that my life was being swept in a flood of brain washing, but I remember with gratitude the fine teachers at the Sofia First Male Gymnasium, who did their best under very difficult circumstances. I studied chemical engineering for about a year—and disliked it. We emigrated to Israel in 1949 where I wanted to study chemistry, but had to wait for about a year as the university chemical laboratories on Mount Scopus were surrounded by the Arab Legion. Slowly academic life improved, but looking back I realize today that I missed the challenges and excitement of a regular university education. Surprisingly, I first tasted the sweet taste of research in the Army. I was attached to a research unit and worked on various projects—mainly on insecticides, as insects had always been a scourge in the Middle East. I found the independence of research to be an addiction from which I do not want to be cured.

ENTERING THE CANNABIS RESEARCH FIELD

A: You published your first paper on cannabis more than 40 years ago. What led you into this field, which at the time was considered of minor interest and importance?

RM: In the early 1960s I returned to Israel from a post-doctoral stay at the Rockefeller Institute in New York, where I worked with the late Professor S. W. Pelletier on investigations on the structure of some plant triterpenes. My PhD thesis (with F. Sondheimer) in the mid-1950s was on synthetic chemistry, mostly in the field of steroids. I found research at the borderline of chemistry and biology fascinating. I believed then, and I still believe, that the separation of scientific fields is just an admission of our limited ability to learn and understand several scientific areas. In Nature the border does not exist. If a leaf and a tree were able to think they

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'that the separation of scientific fields is just an admission of our limited ability to learn and understand several scientific areas . . . If a leaf and a tree were able to think they would not know the difference between chemistry and biology.'

A: And back in Israel?
RM: Back in Israel I was appointed to a junior faculty position in the chemistry department of the Weizmann Institute in Rehovot. In Israel, as in the US and many countries in Europe, new staff members are supposed to choose their own research topics and then, after 5–6 years, their success (or lack of it) is evaluated and the junior staff member obtains (or does not obtain) tenure. I chose to work on several topics on the chemistry and actions of natural products. One of my topics was the constituents of cannabis.

A: Why that topic?
RM: Why cannabis? On reading the old literature on cannabis I was surprised to note that from a modern point of view the field was ripe for a reinvestigation. In the early 1960s it was almost totally neglected. There were 19th-century papers in many languages. Being born in Europe I had to know many languages—including French, German and Russian—in which most of the old cannabis papers were written, which helped me in my literary searches. I found and read dozens of publications in long-forgotten and obscure journals. Then I went to the more recent papers by Roger Adams, a prominent US chemist, and by Lord Alexander Todd, a Nobel Prize-winner, and was surprised to find that in spite of the high level of research conducted in their laboratories, apparently the active constituent(s) of cannabis had never been isolated in pure form and no definite structure(s) had been put forward. The reasons may have been technical. We know today that the cannabinoids—a term I coined some years later—are present in cannabis as a mixture of a large number of closely related constituents, which were apparently difficult to separate by the methods available in the 19th and early 20th centuries. Chromatography methods were well developed at the time I started work and the availability of novel spectrometric methods looked promising for the structure elucidations, which in the field of natural products were, until then, based on laborious chemical degradation work. I assumed that of particular help could be an early type of a nuclear magnetic resonance (NMR) spectrometrometer that was built and used in the physics department. Luckily I was proved right.

A: Why was the cannabis field dormant at the time and why did you think that it was of importance?
RM: The three major illicit drugs derived from plants were then, and still are, opium, coca and cannabis. Morphine had been isolated from opium early in the 19th century and its very complicated structure was elucidated in the 1920s by Sir Robert Robinson. Cocaine was isolated from coca leaves in the middle of the 19th century and the famous chemist Richard Willstatter had been able to describe its unusual structure in the last decade of the 19th century. The availability of pure materials made possible biochemical, pharmacological and clinical work with these important alkaloids. Modern scientists refrain from work on mixtures—and crude plant extracts are complicated mixtures—as the results of such research are difficult to reproduce and interpret. As the active constituent(s) of cannabis was not available in pure form there was very little modern biological and clinical work on it. A further difficulty was a legal one. As cannabis was an illicit substance it was not readily available to most scientists. Even if obtained legally, research with it was a laboratory nightmare. In many countries special security precautions had to be undertaken. In most universities researchers could not follow the security regulations effectively and pharmaceutical companies did not want the presumed notoriety of 'trying to make money out of marijuana'. From a scientific point of view cannabis research had effectively been eliminated.

A: How did you overcome these obstacles?
RM: I was unaware of them. I went to the administrative director of the Weizmann Institute and simply asked him whether he knew somebody at Police Headquarters. After realizing that I was not trying to settle some minor traffic ticket but was requesting starting material for research, he called the head of the investigative branch at Police Headquarters, with whom he had been together in the army. I heard the police officer asking 'Is he (meaning me) reliable?'. On receiving a positive answer, he asked me to come over to Tel Aviv and thus I obtained 5 kg of superb, smuggled Lebanese hashish. I took a bus back to Rehovot, nobody in the bus realizing that the smell from my bag was from hashish. Later we found that both the head of the investigative branch of the police and I had broken quite a few laws. The Ministry of Health was in charge of illicit drug licensing and not the police, and I had broken the severe drug laws. Luckily, being 'reliable', I just had to apologize. May I just mention that since then I have been obtaining hashish from the police for over 40 years, with Ministry of Health-signed documents, without any administrative problems. I still wonder whether the

absence of bureaucracy in my dealings with the regulatory bodies has something to do with the fact that most of the pharmacists working at the Ministry are my ex-students, and they believe that their ex-professor is 'reliable'. Working in a small country certainly has its positive aspects.

DISCOVERY OF THC

A: Going back to science, how did you then proceed?
RM: First, I re-isolated cannabidiol (CBD), a major non-psychoactive constituent which had been isolated by both Adams and Todd, but whose structure was only partially known. Yuval Shvo, a close friend, and I were able to establish its structure and stereochemistry mainly by NMR analysis, using an early NMR machine [1]. The publication on CBD caused no scientific ripples. Over the years, however, interest in CBD has gradually increased. There are hundreds of publications on it now. It is a potent anti-inflammatory agent. A few years ago, together with Ruth Gallily in Jerusalem and Mark Feldmann in London, we found that it lowers the production of tumour necrosis factor (TNF)-α, a potent inflammatory cytokine, and reduces the symptoms of rheumatoid arthritis in a mouse model [2]. Many years previously, in a clinical trial in Brazil, headed by E. Carlini, we found that it is a good anti-epileptic agent [3]. We then prepared and sent to Brazil several hundred grams of CBD, which apparently were not used fully in the epilepsy trial, and the Brazilian group are still using it in research, which has shown lowering of anxiety and therapeutic effects in schizophrenia; and the Mexican group of Murillo-Rodriguez has presented evidence that it leads to awakening [4]. Surprisingly, its mechanism of action is still an enigma. It seems to act through an unknown receptor and recent work by Hillard has shown that it blocks the uptake of adenosine [5]. Together with a group at the Hadassah Hospital here we have noted that it reduces sugar levels in diabetes-prone mice [6], and another group at the same hospital led by R. Durst has submitted a publication on ameliorating the effects of heart ischaemia by CBD treatment. As it has very low toxicity it may become an important drug.

A: And next?
RM: In 1963 another close friend at the Weizmann Institute, Yehiel Gaoni, joined me in the cannabinoid research. Yehiel had recently returned from Paris with a PhD in organic chemistry from the Sorbonne. Our goal was to identify the active constituent of cannabis. We needed a biologist with experience in psychopharmacology who could give us feedback on the activity of fractions and pure compounds isolated. We succeeded in enticing Dr Haviv Edery, the head of pharmacology at the nearby Biological Research Institute. He had emigrated from Argentina a few years previously and knew about the extensive use of *maconha* (South American cannabis) there. He had a colony of rhesus monkeys and all the biological work leading to the isolation of the active hashish component was based on feedback from the rhesus monkeys. Repeated chromatographic separations of a petroleum ether extract finally gave us a pure although oily compound which, however, crystallized as one of its esters. The NMR spectrum and elemental analysis led to its structure and we even succeeded in preparing it from cannabidiol [7]. We named the compound Δ^1-tetrahydrocannabinol (Δ^1-THC), so that its nomenclature would parallel that of CBD. Unfortunately some pedantic chemists decided to follow the strict rules of chemical nomenclature and today Δ^1-THC has become Δ^9-THC.

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A: So the neglect of cannabis research was overcome?
RM: Gradually scientists in various disciplines realized that the cannabis field was ripe for investigation and thousands of publications have since appeared on THC. It is even used as a therapeutic drug against nausea and for enhancing appetite. Surprisingly, it has not become an illicit drug—apparently cannabis users prefer their marijuana and hashish.

A: And other cannabinoids?
RM: Later we isolated six or seven new plant cannabinoids. Over the years many other groups isolated additional compounds—mostly related closely to the original cannabinoids we found in the plant. We were really surprised that from the horrendous cannabinoid soup in cannabis, only Δ^9-THC affected the rhesus monkeys. As none of the rest of the plant cannabinoids reproduced the effects of THC in monkeys, very little work has been carried out on them. This is a mistake. Roger Pertwee in Scotland found recently that one of these compounds is actually a cannabinoid antagonist and may have important medical applications [8]. A student of mine, Yehoshua Maor, made a small change in the structure of a minor plant cannabinoid, named cannabigerol, which we discovered in 1964, and found that that the new compound reduces blood pressure. I believe that the cannabinoids represent a medicinal treasure trove which waits to be discovered.

A: How was your research funded?
RM: Originally we did not need a great deal of support. All the work was performed by Yehiel Gaoni and myself. I

recall that early in 1963 I applied for a grant from the National Institute for Health (NIH), but I was told that they do not support research on cannabis as its use was not an American problem. How little did they know! A year later the head of pharmacology at the National Institute on Mental Health, Dan Efron, called me and asked whether I could see him in a few days. He came over and I understood that a US senator had called NIH and asked whether marijuana would destroy the brain—apparently his son had been seen smoking it. At NIH nobody knew anything about marijuana but they recalled that somebody in Israel had asked for a grant to look for the active constituent. Efron promised financial support, which indeed was granted shortly thereafter, and took with him the entire 'world' supply of THC which we had. This sample of THC was used for many of the original cannabinoid investigations in the United States, although our contribution was seldom recognized. NIH has supported my research with grants ever since for over four decades, although I have to work hard to renew it every few years. I have known most of the directors of the National Institute on Drug Abuse (NIDA). I found that all of them were very knowledgeable in the field and very dedicated to solving the problems of drug abuse and addiction. I am under the impression that much of the basic research in the world in this field is still supported by NIDA. Of course, most of it is conducted in the United States. I was also pleasantly surprised to note that with NIDA the bureaucratic demands were minor and that once a project was approved there was no interference, either scientific or administrative, although our results and those of my colleagues did not always necessarily support the drug policy of the US federal administration. By the middle of the 1960s, in the United States the Flower Generation was blooming, marijuana and even THC had become common words and research money was easy to obtain.

A: What were the next steps in your research?

RM: First, Gaoni and I accomplished and published facile syntheses of almost all natural cannabinoids [9]. However, these procedures were not always easy to procure—on my visits to the US West Coast I noted that in many libraries the appropriate pages in the *Journal of the American Chemistry Society* were neatly cut out. The librarians told me that apparently some students found them quite useful, although not necessarily for academic purposes. The next major problem seemed to be the metabolic pathways of THC. In a review article in *Science* I bravely stated:

> In the absence of definite evidence, one can speculate that a metabolite and not THC is in fact the active compound on the molecular level. Habitues say that marijuana has no effect when used for the first time. While the basis of their observations may be psychological, it is also possible that that it is due to a biochemical phenomenon. If the hydroxylation enzyme were an inductive one then the initial administration of marijuana may be the triggering act for its formation [10].

A: Other research groups also because interested in this question?

RM: It seems that about every major group in the field had the same idea. In 1970 four laboratories including mine, now at the Hebrew University Medical Faculty, reported more or less simultaneously that hydroxylation at the 11-position was the primary metabolic step. Synthetic 11-hydroxy-Δ^8-THC, as predicted, sedated Edery's rhesus monkeys even better than THC itself. Other primary metabolites, such as 8-hydroxy-Δ^9-THC and hydroxylated derivatives on the side chain, were also found to be active, but for some obscure reason never became as popular in research as 11-hydroxy-THC. A few years later, with Agurell's group in Sweden, we found that Δ^8-THC-11-oic acid is also formed [11]. As it is excreted in the urine (as the glucuronide) over many weeks it is the analytical target for analysis of cannabis use. Almost all radioimmunoassay methods used this acid—and we had forgotten to patent it! A huge amount of work was conducted on the cannabinoids over the next 15 years by my group, now at the Hebrew University of Jerusalem, and by many other groups, mainly in the United States, Europe and Japan. We learned a great deal about cannabinoid pharmacology, biochemistry and clinical effects; however, their mode of action remained an enigma.

A: Why did their mode of action remain an enigma? Was there something unusual?

RM: The reasons for this baffling situation were both technical and conceptual. On the technical side it was noted that THC is active in both enantiomeric forms (although with a different level of potency) and this was incompatible with action on a receptor, which will usually bind one stereoisomer only. However, all the work on the stereospecificity of cannabinoid action had been performed with THC synthesized according to a procedure published by our group based on commercial α-pinene [9]. We knew that commercial pinene was not stereochemically pure and therefore led to stereochemically impure products. Hence, the lack of streospecificity could be due to the presence of the active (–) stereoisomer in the presumed pure (+) isomer. So we repeated the synthesis with stereochemically pure (+) α-pinene and tested the (+) THC produced. It had no (–) THC-like activity, as expected. Then we tried this again on a much more active

synthetic cannabinoid, HU-210, which is at least 100 times more active than THC. Its enantiomer, HU-211, turned out to be inactive in a wide series of tests donperformede in collaboration with my friends Billy Martin, Toby Jarbe and Allyn Howlett.

The conceptual problem related to THC activity had been raised by Bill Paton from Oxford, who had pointed out that the cannabinoids belong to the group of biologically active lipophiles, and that their effects should be compared with the chronic effects of anesthetics and solvents. Hence, following this line of thought, it was possible to explain the action of THC without postulating the existence of a receptor or specific action on an enzyme or a biological system.

A: But then evidence for a receptor site came through?
RM: In 1988 Allyn Howlett, with her then graduate student Bill Devane, brought out the first evidence that a cannabinoid receptor exists in the brain [12]. We assumed that a cannabinoid receptor is not formed for the sake of a plant that has compounds that bind to it, but for an endogenous brain ligand. I decided to try to identify it.

THE DISCOVERY OF CANNABINOID LIGANDS

A: The discovery of the cannabinoid ligands is an important landmark in cannabinoid research. How was that achieved?
RM: Bill Devane had by this time completed his PhD thesis and applied for a post-doctoral position in my laboratory. He wanted to learn some synthetic chemistry; I had other plans for him. We first synthesized a novel, highly active radioactive probe (so Bill acquired synthetic experience), and proceeded towards the identification of a cannabinoid ligand using this novel radioactive probe. Later, a visiting fellow from the Czech State, Dr Lumir Hanus, joined my group. Over the next 18 months Bill and Lumir tried to solve the isolation problems associated with the endogenous cannabinoid ligand. Because of the lipophilic nature of the plant cannabinoids, we assumed that the brain ligands are also lipids; or, perhaps, we simply wanted them to be lipids, as the laboratory had experience with such compounds, but we did not know how to deal with peptides.

A: Sounds difficult!
RM: The isolation problems were at first almost insurmountable. As soon as fractions which bound to the cannabinoid receptor were purified, they started to lose their activity. We know now that this was due to the lack of stability of the cannabinoid ligand. Ultimately we had a miniscule amount of material which seemed pure and tried to obtain a NMR spectrum. This was not simple to do on the 300 MHz machine available to us, but we let the spectrum be run over a weekend and we ended with a curve which contained probably more impurities than actual material. However, two groups of peaks clearly indicated olefinic and doubly allylic protons in a ratio of 4 : 3. Such spectra are quite typical for polyunsaturated long-chain fatty acids. For me this was the breakthrough—we had a polyunsaturated fatty acid derivative, possibly an arachidonic acid derivative.

A: Exciting—what next?
RM: Then with the help of a colleague at the Technion in Haifa, Asher Mandelbaum, we obtained a high-resolution mass spectrum which indicated that the molecule contained a nitrogen atom, certainly not a common feature in fatty acids. However, the structure was now close at hand. Some more mass spectra and a better NMR led to a final formulation of anandamide as it stands today [13]. We were also interested in some tests which were closer to physiological reality than just binding to a receptor, but with the miniscule amounts of endogenous material we had from the brain, we obviously could not perform *in vivo* work. However, Roger Pertwee in Scotland had reported experiments on inhibition of the electrically evoked twitch response of mouse deferens which required very small amounts of material. We sent him some (impure) material and within a few days he happily informed us that this material paralleled THC in activity. However, when we sent him pure anandamide it was inactive. Later it emerged that the pure anandamide had oxidized on its trip from Jerusalem to Aberdeen; the impure material obviously contained an antioxidant.

A: How did you name this newly discovered substance?
RM: We decided to name the new brain-derived ligand anandamide. Bill was learning Sanscrit at the time and suggested 'ananda' (supreme joy in this ancient tongue). This portion of the name certainly fits the 'amide' moiety of the structure. We believed then—and still do—that the endocannabinoid system plays a role in the formation of emotions. I looked for a suitable Hebrew equivalent but nothing came to mind. There are many synonyms for 'sorrow' in Hebrew but considerably less for 'joy'. In any case, anandamide certainly brought joy to us: it has been cited over 1800 times and its effects are studied widely.

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A: Your group later isolated 2-AG. What was the background to its identification?

RM: Sean Munro in Cambridge had isolated a second receptor in spleen, which was absent in brain. I asked a new PhD student, Shimon Ben-Shabat, to try to find the peripheral ligand that activates this receptor. In a few months he had an active mixture which, however, bound to both receptors. The mixture contained no fatty acid amides but had three fatty acid glycerol esters, one of which—obviously the arachidonoyl one—was found to bind to the receptors. Its binding potency was much lower than that of anandamide and we were quite uncertain of its role as a cannabinoid ligand. By 'we' I mean our team of 15 colleagues—my group, that of Zvi Vogel in Rehovot, who performed some of the binding, Roger Pertwee who looked at the contractions of vas deferens, Norb Kaminski who worked on cAMP and Billy Martin in Richmond, who performed the animal pharmacology [14]. Today we know that the low binding was due to the unsuitable *in vitro* conditions we used. Now we have values which parallel those of anandamide and we also know that the inactive fatty acid esters which accompany 2-AG strongly enhance its activity, and that this 'entourage' effect may be general with endogenous cannabinoid ligands.

I also made a rather unbelievable mistake. I was under the impression that Lumir Hanus, who was on vacation in Prague when I wrote the paper, had told me that he could not see any 2-AG in brain and I stupidly added a sentence stating this. I did not check his laboratory notes (in Czech). Later Sugiura in Japan and Piomelli in California made us blush, as they found large amounts of 2-AG in brain. Lumir had not even looked at that point for 2-AG in brain.

THE COMPLEXITY

A: There are numerous additional endocannabinoids known today. They act on a long list of biological targets. Can you summarize today's situation?

RM: Other groups, as well as mine, have indeed identified various fatty acid ethanolamides and glycerol esters as well as fatty acids amides of amino acids. Some of the new members of this family of compounds bind to the CB1/CB2 receptors. Others do not; but new cannabinoid receptors are also being discovered. An orphan receptor, GPR55, has been found to bind anandamide and 2-AG, but not some synthetic cannabinoids that are excellent ligands to CB1/CB2. On the other hand, palmitoyl ethanolamide, a potent anti-inflammatory agent, which does not bind to CB1/CB2, binds to GPR55 [15]. We also reported recently that arachidonoyl serine, present in brain, is a vasodilator [16].

A: It seems as if one is dealing with a wide family of substances?

RM: I believe that we should look at the endogenous fatty acid ethanolamides and glycerol esters, as well as the fatty acids amides of amino acids as members of a large endocannabinoid family. Most of them seem to be formed 'on demand' and their actions take place around the areas of synthesis. Hence their effects are predominantly local and specific. Their actions are ubiquitous. They are involved in most physiological systems that have been investigated—the nervous, the cardiovascular, the reproductive, the immune system, to mention a few. One of their main roles is neuroprotection [17], but over the last decade they have been found to affect a long list of processes, from anxiety, depression, cancer development, vasodilation to bone formation and even pregnancy [18]. Over the last few years several groups have noted that the CB2 receptor is also formed in the brain as a reaction to numerous neurological diseases and is apparently activated by the endocannabinoids as a protective mechanism.

A: Do you still have contact with young scientists?

RM. I still teach graduate students at the Hebrew University of Jerusalem. I have an enthusiastic bunch of young people working in my group. Most are from Israel, but a German and an American have just joined my group. At present my group is a 'mixed bag' of researchers: Moslem and Christian Arabs, observant and non-observant Jews. They work together very well indeed. It is a tragedy that Israelis and Palestinians cannot get along as well as my students do. My teaching does not have defined borders—I teach both chemistry and biology. As I said earlier, I do not believe that Nature has such borders. We have created artificial frontiers, because we do not have the intellectual capacity to learn several fields as there is too much information in them. This is certainly true for neuropsychopharmacology. We can study the physical, neuronal side of neuropsychopharmacogy as well as the psychological aspects. We are not always able to make a connection between them. The field of emotions is one of these fields; but I hope that some day we shall be able to understand fully both the chemistry and neuropsychological mechanisms of emotions, and will realize that they represent two aspects of the same phenomenon.

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