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The Domino Effect: Ed Domino's early studies of Psychoactive Drugs

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ABSTRACT

University of Michigan Pharmacology Professor Ed Domino is an expert in the field of neuropsychopharmacology. For over six decades, Dr. Domino has made many contributions to our understanding of psychoactive drugs, but is most well-known for his role in the development of ketamine anesthesia. This article covers the story behind this discovery, along with many other fascinating personal and professional anecdotes, all of which provide insight into the career of a remarkable scientist.

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Ed Domino was born in Chicago in 1924 into what he described as a lower-middle-class, Polish neighborhood. When the war interrupted life in 1943, he was trained as an electronics technician in the Navy. He went on to study electrical engineering and pre-medicine at the University of Illinois and was awarded B.S. degrees in 1948 and 1949. Two years later, he was awarded his M.D. as well as a master's degree in pharmacology. His knowledge of electronics paid dividends after the war. The University of Illinois was looking for someone who could put together an EEG machine. This landed him a position as a part-time pharmacology instructor. From 1951–1953, he taught classes while working as an intern at the Presbyterian Hospital in Chicago. It was here that his passion for neuropsychopharmacology crystallized.



Why neuropsychopharmacology?

During his service at the Presbyterian Hospital, Ed cared for many cancer patients with inoperable tumors. Pain management was a high priority. Typically, patients were prescribed morphine, but the new and experimental analgesic Dromoran was being used at the time. Dromoran is the racemic mixture of levorphanol and its R-isomer. Ed ordered Dromoran for a female patient with disseminated breast cancer. She was in constant and severe pain, so he had her on a heavy dose. A few days of the treatment passed, and her condition was deteriorating. While off-duty at home, Ed got an emergency call from the nurses. The female

patient was breathing, but only a few times per minute. He dropped everything and rushed to the patient's bedside. She was comatose and in critical condition. Ed began to ventilate her immediately. Although he was giving the patient therapeutic doses of Dromoran, he made a near-fatal mistake. The female patient had a damaged liver that was clogged with cancer. As a result, she was not metabolizing the Dromoran properly. Each consecutive dose was accumulating, and she was on the verge of death.

Amidst the panic, he remembered a recent study about nalorphine, a novel opioid antagonist. Ed had been studying the effects of nalorphine on dogs in the pharmacology department. He instantly got on the phone with his attending physician.

"I think I overdosed your patient with Dromoran. There is a treatment. It's just been published. As far as I know, the only source of the narcotic antagonist in the Chicago area is in the dog lab at the University of Illinois. The patient is terminal and has no relatives from whom to get permission," he said (Gillin 1995). The attending agreed they had no other choice. After retrieving the nalorphine from the lab, Ed injected it into the comatose patient. It worked (Domino, Pelikan, and Traut 1953). In a scene worthy of cinematic recreation, the patient began breathing heavily and screamed out in pain. The nurses and attending physician were stunned. The experience was so potent and dramatic for Ed, he was forever hooked on neuropsychopharmacology.

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Figure 1. Illustration of Dr. Edward Domino. Courtesy of Andreas von Buddenbrock.

Shortly after the nalorphine experience, Ed (See Fig. 1) was becoming fed up with his living situation in the Chicago area. He was working very hard, but the effort wasn't translating financially. After securing a professorship at the University of Michigan, he now needed to obtain funding for his research. Ed's chairman, Maurice "Mose" Seevers, was contracted by the Michigan-based pharmaceutical company Parke-Davis to help when a complex pharmacological problem occurred. The problem at the time was 1-(1-phenylcyclohexyl)piperidine, more commonly known as PCP.

Phencyclidine (PCP)

Dr. Victor Maddox was a Parke-Davis medicinal chemist trying to synthesize a new analgesic. He began to react α -aminonitriles with the Grignard reagent Phenylmagnesium bromide. Unknown to him at the time, Maddox had caused a Bruylants reaction, resulting

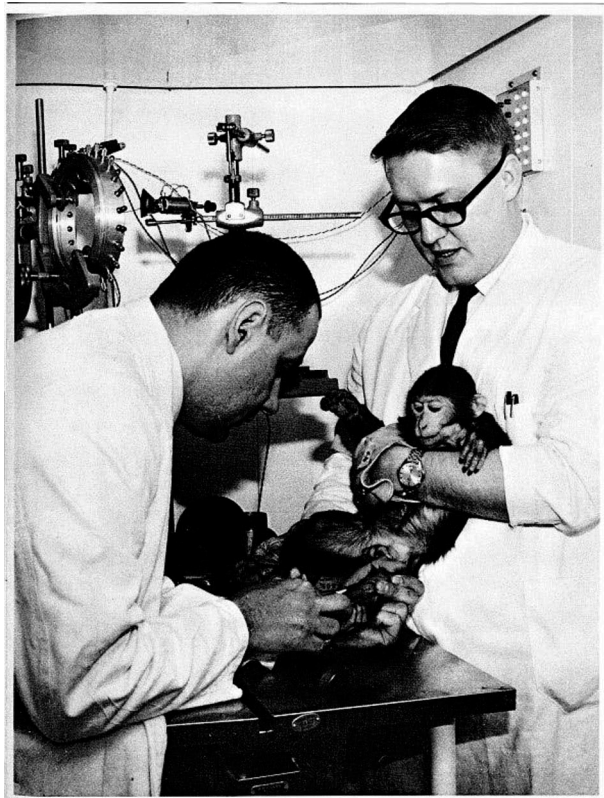


Figure 2. Ed Domino and his colleague are seen performing a pharmacology experiment on a monkey at the Lafayette Clinic in Detroit Michigan. Courtesy of the University of Michigan Bentley Historical Library.

in a new molecule (1-(1-ethylcyclohexyl)piperidine) (Maddox 1981). This sparked his curiosity, and he then reacted 1-piperidinocyclohexanecarbonitrile (PCC) with the Grignard. On March 26, 1956, PCP was born (Maddox, Godefroi, and Parcell 1965). Maddox then submitted the compounds for testing to Parke-Davis pharmacologist Dr. Graham Chen. Using pigeons and cats, Chen noticed that low doses of PCP caused what he called "a state of catalepsy" (Chen 1965; Chen et al. 1959). About a week after first receiving the compound, Chen called Maddox and told him that PCP was the "most unique compound he had ever examined" (Domino 1980). Once the anesthetic potential of PCP was realized, Parke-Davis began a persistent pursuit into the properties of PCP and related arylcyclohexylamines.

In late 1956, Dr. Calvin Bratton (head of pharmacology at Parke-Davis) contacted Mose Seevers and asked if Michigan Pharmacology would analyze PCP in rodents and monkeys. After Seevers got word of the new and interesting cataleptoid anesthetic, he told Ed Domino to investigate the drug (See Fig. 2). In Domino's own words, "I just had to earn a living for

nine months' salary and the chairman had a grant from Parke-Davis. Therefore, I must work on Parke-Davis compounds" (Domino, personal communication, 2017).

When Ed gave low-dose PCP to canines, he found that it caused severe delirium. But in monkeys, it proved to be an anesthetic (Domino 1964). The novel anesthetic was well-tolerated in animal and human studies (Chen et al. 1959; Greifenstein et al. 1958; Luby et al. 1959). PCP was approved and patented for clinical use as a general anesthetic in 1963 under the trade name Serynl® (Godefroi, Maddox, and Parcell 1963). The drug was short-lived, however, due to the unpredictable occurrence of adverse effects, the most notable being a state of "prolonged emergence delirium" (Luby et al. 1959). Although it had a much wider therapeutic index than the available general anesthetics, the acute post-surgery psychosis proved to be too much, and PCP was voluntarily withdrawn from the market as a human anesthetic in 1965 (Domino 2010).

Ketamine

Parke-Davis was long aware of PCP's shortcomings and began working on the development of safer and shorter-acting derivatives years prior to the market withdrawal. As Domino noted, "In the late 1950s into the 1960s, at least 30 Parke-Davis people were assigned to making better PCP derivatives which were short acting, less convulsant and less delirium inducing" (Domino 1980). Dr. Calvin L. Stevens was one of the 30. In 1962, while producing ketone analogs of PCP, the Stevens' lab synthesized a number of aryl-aminocyclohexan-2-one-based derivatives (Morris and Wallach 2014). The derivatives were then screened in rodents and monkeys by Ed Domino and Parke-Davis pharmacologists (Chen, Ensor, and Bohner 1966; McCarthy et al. 1965). The best derivative screened in this process was ketamine (See Fig. 3).

Ketamine passed through the animal studies and was found to be a short-acting anesthetic with a high safety profile. Stevens tricked Parke-Davis by applying for a patent on his own. He succeeded in 1963, and the first ketamine patent was filed in Belgium (Stevens 1963). Parke-Davis was furious with Stevens, a legal battle ensued, and they reluctantly settled with Stevens to claim the rights to their promising new anesthetic. This resulted in U.S. patent 3,254,124 (Stevens 1966). Ketamine was then given a clinical investigation number (CI-581) and prepared for human experiments.

In early 1964, Dr. Alex Lane (head of clinical pharmacology at Parke-Davis) was looking for someone to do the human studies with ketamine. Since he was an



Figure 3. A 10 mL vial of Ketalar®, the former Parke-Davis trade name for ketamine HCl. Ketamine was first synthesized in 1962 by Calvin Stevens, another consultant to Parke-Davis and Professor of Organic Chemistry at Wayne State University. It was originally called "Keet-amine" by Stevens, due to the presence of a ketone group. Courtesy of the AAGBI Anaesthesia Heritage Centre.

M.D. and did some of the animal work with PCP and ketamine, Ed Domino was Lane's first choice. After recruiting Dr. Guenter Corssen from the anesthesiology department down the hall, Ed needed to find a group of subjects and a research facility. He would find everything he needed at the Jackson State Prison in Michigan. A human ethics committee was formed between the University of Michigan, Parke-Davis, and the Upjohn Company (another Michigan-based pharmaceutical corporation). The committee devised an extensive protocol to conduct clinical trials on prison volunteers under ketamine anesthesia. In fact, according to Ed, "To this day, NIH guidelines for prison research are based on what happened here" (Domino, personal communication, 2017).

The prisoners given anesthetic doses of ketamine consistently maintained good blood pressure, respiration rate, and other vital signs. The drug also showed a much shorter duration of action than its predecessor, phencyclidine. Ketamine's safety profile was unprecedented. The chance of an anesthetic dose resulting in death was significantly lower when compared to ether and other general anesthetics in use before ketamine. It was proving to be a remarkable compound, except for one thing. As the prison

volunteers emerged from anesthesia, they were experiencing the same form of sensory dissociation that PCP caused. Ed was both confused and fascinated by this effect. Like any good scientist, he decided to socialize his curiosity. His favorite person to share these curiosities with was his wife, Antoinette (Toni) Domino. He was devoted to involving her in everything he did, including science. One day, when talking about ketamine's strange effects, Toni Domino would change the course of pharmacology forever. According to Ed, "We saw in humans exactly what we saw in monkeys. Except for one thing. When the humans recovered from the anesthetic agent—while in recovery they said, 'Jesus, I'm in outer space. My God, I don't have any arms or legs, I'm floating, man what a high! Oh my God!' We reported it right away to the Parke-Davis people and they said, 'Ed, this drug will produce a high that they like.' I said, 'Well what kind of high?' Well, it turns out they feel their arms and legs but when they take the drug and don't touch themselves, they feel as if they have no arms or legs. Like floating on clouds. I talked to my wife about that and I said 'Honey, I'm dealing with this goofy compound, beautiful anesthetic, but it gives people a high. They're disconnected from their environment somehow.' Toni then said, 'You mean there's some kind of dissociation? Why don't you call it a dissociative anesthetic?'" (Domino, personal communication, 2017). Ed suggested the term in his 1965 paper and the rest is history (Domino, Chodoff, and Corssen 1965). Dissociative anesthetics have since been a bona fide class in pharmacology, and a reminder to listen to the people around you. Ketamine-HCl was approved by the FDA in 1970 and sold by Parke-Davis under the trade name Ketalar®. Due to its short-acting analgesic properties, ketamine made its debut on the battlefields in Vietnam. It would become the most widely-used battlefield anesthetic in the Vietnam War. This wasn't the first time the U.S. military reaped the benefits of Ed's pharmacology skills.

Cracking the cannabinoid code

During the 1950s, the U.S. military invested considerable resources into developing non-lethal incapacitating agents. The epicenter of this effort was a facility in Aberdeen, Maryland, called the Edgewood Arsenal. From 1948 to 1975, the U.S. Army Chemical Corps conducted human experiments using a range of psychoactive substances (Ketchum 2006). While the human testing was going on at the Arsenal, much of the basic science work was contracted out to universities. Chairman Mose Seevers was an international

authority in pharmacology at the time. He had numerous contracts with corporations and government institutions, and the Michigan Pharmacology Department was doing work for the Edgewood Arsenal (Domino 2007). Among the array of psychochemical weapons of interest were synthetic cannabinoids. In a serendipitous way, synthetic cannabinoids and cannabis would end up playing a substantial role in Ed's early research.

N: Speaking of marijuana. I have a question about some of your work with synthetic cannabinoids.

ED: Ohh! Now you're talking. Everything I've done it's not because of me, it's because I needed to earn a living.

N: I've been reading about the Edgewood Arsenal and a lot of the work the military was doing on incapacitating agents.

ED: Beautiful story that also has to do with my Chairman Mose Seevers. He was a consultant to the Edgewood Arsenal. I'll never forget that he got a secret contract in which people like me could get some of their salary for research through that. With no idea of what we're dealing with.

N: So, a bottle with a code name?

ED: Yes, just a bunch of code names. But with a bunch of goofy oils

N: Red oil?

ED: Yeah. We even had a problem of how the heck to get these stupid oils into solution to inject in the animals. In fact, Harry Hardman, another guy who was in Pharmacy that ended up going into Pharmacology—he developed a method of getting these oils into a suspension that we could then inject into animals. They were the most remarkable agents when we'd give them to the animals. Some of these red oil compounds would put a monkey into a state of hibernation, lowered blood pressure, lower temperature, a state of artificial hibernation, for up to a week!

N: A week?!

ED: I'm not kidding you. Some of those red oil compounds, you give them to a dog or a monkey and they'd be anesthetized 24 hours a day. Occasionally, you would have to move them gently back and forth or so. You know you're always taking care of them and basically, they'd recover in a few days to a week depending on the dose.

N: Could they be awoken from the hibernation with stimulation?

ED: Well, a little bit, not so much.

N: All you knew about it was a number or a code name?

ED: Yes, except I'll never forget I got one of the red oil numbers and it had the molecular formula on the bottle.

N: Somebody left the formula on the bottle?

ED: I looked at that thing and was talking to Harry Hardman and said, "Harry, there's no damn nitrogens in this stuff. Carbons, hydrogens, oxygens, no nitrogen." Harry writes down the formula and says, "I'm going over to the Chem Library to see if I can plug this into the chemistry library's list of all the chemicals in the world." He comes back and says, "Ed these things are marijuana derivatives." I said, "What the hell do you mean?" He said, "They are derivatives of THC." I said "Really? Jesus Christ, we better tell our chairman." So, we go up and make an appointment to see Seevers. We said, "Dr. Seevers, we have this bottle that has the molecular formula on it, with no nitrogen. We went to the chemistry library and they told us it's a synthetic cannabinoid." Seevers says, "Jesus Christ! Sons of bitches, as of right now, I want you to keep your mouths shut!" Immediately gets on the phone and calls the head of Edgewood Arsenal—the guy that's heading all the research. Seevers says, "I got these two guys, Ed Domino and Harry Hardman. They cracked the goddamn code on these compounds. These are synthetic cannabinoid derivatives, what the hell do we do?" Head of Edgewood says, "Alright, I'll immediately swear them to secrecy." Over the phone, I had to give my name and say, "I swear. . .," you know. Here we are sitting in the chairman's office and the guy from Edgewood Arsenal makes us swear that we will never divulge what we're dealing with. And we were dealing with cannabinoids.

ED: Eventually, after many years, that project stopped. By the way, those compounds were given to humans.

N: Right! At the arsenal (Sidell et al. 1973).

ED: After we did the animal work here, the Arsenal got some of the soldier volunteers to take these drugs. These guys would take them and be spaced out for days.

N: Close to a week, right!

ED: Yeah, so the Edgewood Arsenal decided that these were super-potent cannabinoids, and maybe they should just drop the project. Eventually they did and decided that we could publish on it. And we did. [author's note: see Hardman, Seevers, and Domino 1971a, 1971b].

ED: After publishing the work on marijuana derivatives, I got a reputation for being good in

marijuana research. Jack Gottlieb, who was head of Psychiatry at the Lafayette clinic [a state-funded mental health clinic in Detroit], calls me up and says, "Ed, I'm getting in trouble with the Michigan Legislature. We're having everyone smoking pot and nobody knows what the hell it's all about. Can you do any research on pot?. You've done it on all these synthetic derivatives in animals, how about doing pot research in humans?" I said, "Sure, why not?" He said, "The only place that's legal in the state of Michigan to smoke marijuana is the Lafayette clinic in Detroit." Under the law that created the Lafayette clinic, they said that you could do substance abuse research that included marijuana. As a result, I had a legal source which I got from the NIH, and I could do the work in the Lafayette clinic. The next thing was, where am I going to get my volunteers? Turns out that was damn easy. All I did was go to the *Michigan Daily*. I said, "I'm doing a study on marijuana at the Lafayette clinic, it's all legal, I can get legal marijuana to do studies in normal volunteers. If you're interested, we can pay you so much for coming in." What we would do is drive you to the clinic in Detroit at the end of the day, get you high at the only legal place in the state of Michigan, and then drive you back. I had volunteers coming out of my ears. I was loaded with students here at Michigan that wanted to get high. My wife and I have five kids, so I had a big station wagon. I would load it up with volunteers and I'd drive them to the Lafayette clinic.

N: You drove them yourself in the family station wagon?

ED: Yup! My job was to drive them down there, get them high, run the study, and bring them back. In fact, I had to deposit each volunteer at their house, so that it was all legal. They promised that after they got back to Ann Arbor they would go home and sleep it off. Only the next day would they return to normal things. It was all approved by the human use committees. And that's how I got involved in marijuana. I did dozens and dozens of marijuana studies (see Domino 1971; Domino, Rennick, and Pearl 1974) (See Fig. 4).

Ketamine as an antidepressant?

ED: They loved me at the Lafayette clinic. This [human cannabis studies] also gave me a

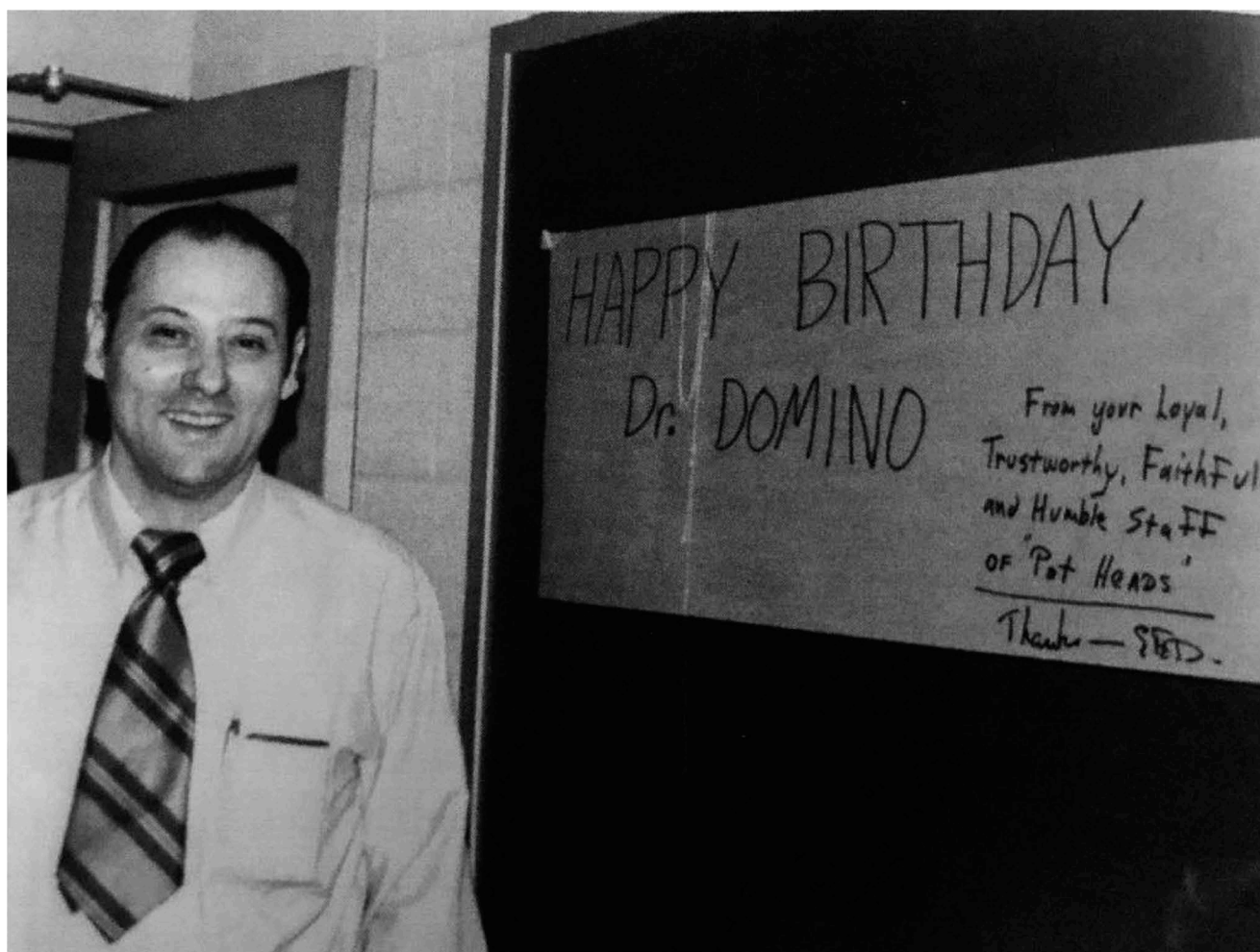


Figure 4. Ed Domino is seen smiling next to a sign his colleagues put up in honor of his birthday. The sign reads “Happy Birthday Dr. Domino. From your Loyal, Trustworthy, Faithful and Humble Staff of Pot Heads.” Courtesy of Dr. Ed Domino.

reputation that I’m good in drug abuse. As a result, they used to send all the drug abuse patients to me. Usually one day a week, typically Thursdays, I’d have a clinic day seeing patients.

N: This was psychiatric work?

ED: Yes, I was a clinical pharmacologist working with patients in drug abuse.

N: Interesting.

ED: Years ago, many young people were getting “high” from the dissociative effects of low-dose ketamine. I remember a few different patients, but one woman I’ll never forget. She was a young and beautiful lady who had become a ketamine abuser. She was using ketamine every couple of weeks. The psychiatrist that referred her to me asked if I could advise him on how to properly treat the patient. I met with her and went through the history of how much ketamine she was using. She was not using too much

ketamine, and not too often either. Every couple of weeks she used the standard dose that will produce a “high.” So, I said to her, “why are you involved with this kind of funny business with ketamine?” She said, “Oh Doctor, I’m so depressed.” I said, “Well what about some of the drugs that we have for depression?” She said “Well, the psychiatrist put me on different antidepressants and nothing worked. Somehow, I’m resistant and I have a terrible depression. But you know, I got ‘high’ once on ketamine and after that, I was no longer depressed for about a week or two.” I said, “What? You mean you’re taking ketamine because you’re depressed?” She responded, “Oh Doctor, I’m so depressed I’ll take anything that works.” Dumb me, I said, “Well this obviously is not good for you in the long run. You can’t get ‘high’ to have an antidepressant effect. This is not a good combination. I

think in the long run it would do you more harm than good. My advice is that your psychiatrist taper you off the ketamine and try to add a combination of different antidepressants.”

N: So that was the first time you got a taste of ketamine’s antidepressant effects?

ED: Yes, I talked to my wife about it and said, “This is a crazy drug, you get ‘high’ and feel good for a period after. This will never work.” Dumb me, dumb me!

N: What year was this?

ED: About 35 years ago. This was a time that I was active in clinical research at the Lafayette Clinic. I also ran a drug testing laboratory. I’ll never forget that ketamine story. I really thought the concept of getting a “high” and then having an antidepressant effect made no sense. Why didn’t I choose to study that further? The idea was lost until a friend of mine by the name of John Krystal, a psychiatrist at Yale University, was studying ketamine as a schizophrenomimetic drug. His research surprisingly showed that ketamine had an antidepressant effect in some volunteers. I was amazed after reading John Krystal and his colleagues’ publication. We had a lot of depressed patients at the Lafayette Clinic and it would have been easy for the psychiatrists to test low-dose ketamine as an antidepressant 35 years ago. If only I had listened to the patients!

The use of low-dose ketamine as a treatment for major depression and bipolar disorder is of interest to the medical community. Heavily involved in this research, Ed is currently collaborating with colleagues across the globe to elucidate the antidepressant mechanism and develop safer and more efficacious ketamine derivatives. The world became different on August 3, 1964—the day Ed administered the first intravenous dose of ketamine to a human (Domino, Chodoff, and Corssen 1965). Ketamine is still being used in operating theaters around the world. From the battlefields of Vietnam to the dance floors in Hong Kong, both medically and culturally, ketamine will continue to have a positive impact.

Ed Domino’s passion for pharmacology and dedication to collaboration have led him to publish over 800 scientific articles or book chapters. Dr. Domino is both an outstanding scientist and human being, whose legacy should be preserved (See Fig. 5). “The Domino Effect” is known as a chain reaction of falling dominoes, whose cumulative effects can be traced back to actions of the first, single member. When properly aligned, a row of dominoes can only be stopped by a

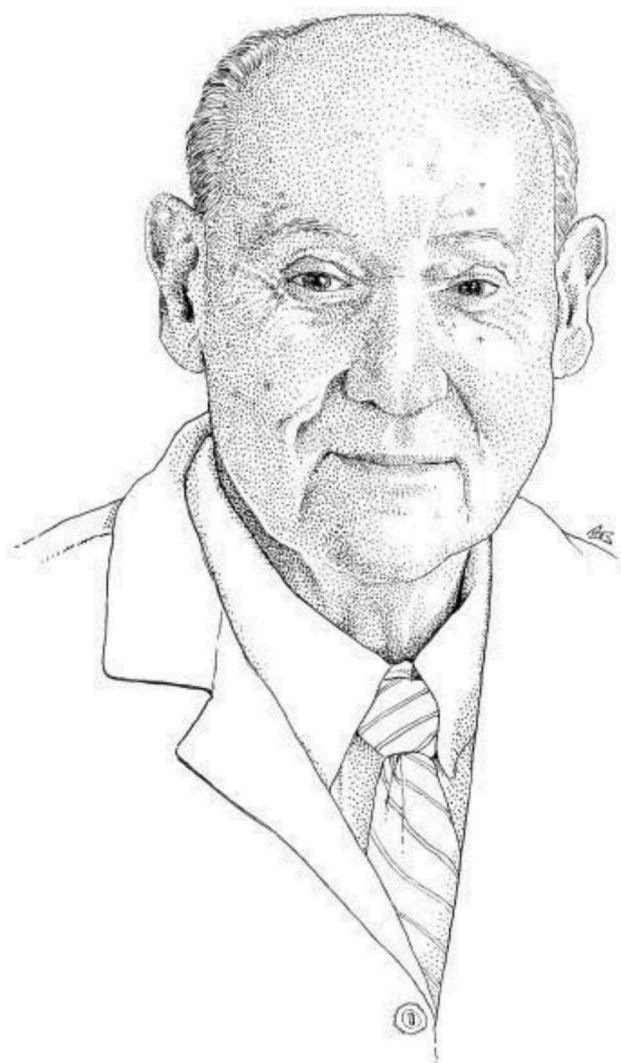


Figure 5. Illustration of Dr. Edward Domino. Courtesy of Andreas von Buddenbrock.

lack of dominoes in line on which to lean. His family, friends, colleagues, postdocs, medical students, graduate students, and all human beings inspired by Ed’s life represent an infinite row of dominoes.

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