

FEATURE

He Was a Science Star. Then He Promoted a Questionable Cure for Covid-19.

The man behind Trump's favorite unproven treatment has made a great career assailing orthodoxy. His claim of a 100 percent cure rate shocked scientists around the world.

By Scott Sayare

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When diagnosing the ills afflicting modern science, an entertainment that, along with the disparagement of his critics and fellow researchers, he counts among his great delights, the eminent French microbiologist Didier Raoult will lightly stroke his beard, lean back in his seat and, with a thin but unmistakable smile, declare the poor patient to be stricken with pride. Raoult, who has achieved international fame since his proposed treatment for Covid-19 was touted as a miracle cure by President Trump, believes that his colleagues fail to see that their ideas are the products of mere intellectual fashions — that they are hypnotized by methodology into believing that they understand what they do not and that they lack the discipline of mind that would permit them to comprehend their error. “Hubris,” Raoult told me recently, at his institute in Marseille, “is the most common thing in the world.” It is a particularly dangerous malady in doctors like him, whose opinions are freighted with the responsibility of life and death. “Someone who doesn’t know is less stupid than someone who wrongly thinks he does,” he said. “Because it is a terrible thing to be wrong.”

Raoult, who founded and directs the research hospital known as the Institut Hospitalo-Universitaire Méditerranée Infection, or IHU, has made a great career assailing orthodoxy, in both word and practice. “There’s nothing I like more than blowing up a theory that’s been so nicely established,” he once said. He has a reputation for bluster but also for a certain creativity. He looks where no one else cares to, with methods no one else is using, and finds things. In just the past 10 years, he has helped identify nearly 500 novel species of human-borne bacteria, about one-fifth of all those named and described. Until recently, he was

perhaps best known as the discoverer of the first giant virus, a microbe that, in his opinion, suggests that viruses ought to be considered a fourth and separate domain of living things. The discovery helped win him the Grand Prix Inserm, one of France's top scientific prizes. It also led him to believe that the tree of life suggested by Darwinian evolution is "entirely false," he told me, and that Darwin himself "wrote nothing but inanities." He detests consensus and comity; he believes that science, and life, ought to be a fight.

It is in this spirit that, over the objections of his peers, and no doubt because of them, too, he has promoted a combination of hydroxychloroquine, an antimalarial drug, and azithromycin, a common antibiotic, as a remedy for Covid-19. He has taken to declaring, "We know how to cure the disease." Trump was not the only one eager to embrace this possibility. By the time I arrived in Marseille, some version of Raoult's treatment regimen had been authorized for testing or use in France, Italy, China, India and numerous other countries. One in every five registered drug trials in the world was testing hydroxychloroquine.

In March, Raoult announced that his hospital would test and treat anyone who cared to show up. Crowds gathered at the entrance to the IHU in winding single-file lines, like pilgrims shuffling toward their private audience with the oracle. On March 16, Raoult released the results of a small clinical trial that showed, he said, a 100 percent cure rate. The study has since been widely debated, and Raoult's boosterism has been lamented by scientists and health officials around the world; in a comment more or less representative of the tenor of the controversy in France, where Raoult's name and image have now been everywhere for weeks, one detractor, a generally thoughtful politician, suggested that Raoult "shut his face and be a doctor" and that he "stop saying 'I'm a genius' all over the place."

His colleagues liken his psychology to that of Napoleon, though he is not physically small. When asked by one journalist about his tendency to "swim against the current" of scientific thought, Raoult responded: "I'm not an 'outsider.' I'm the one who's farthest out in front." Axel Kahn, a geneticist and physician who has known Raoult for nearly 40 years, told me that he has always been this way. "One of Professor Raoult's abiding characteristics is that he knows that he's very good," Kahn told me. "But he considers everyone else to be worthless. And he always has. It's not a recent development." At his home, alongside a collection of Roman busts, he is said to keep a marble statue of himself.

Raoult, who is 68, is a sturdily built but fine-featured man, with high cheekbones and a tight, contemptuous mouth. In recent years, he has hidden these behind a straggly white mustache and goatee and has grown his flaxen hair down to his shoulders. On his right

pinkie he now wears a silver skull. In internet memes, he has been depicted as the wizard Gandalf and as a druid; except for his white lab coat, he has the general aspect of a fortuneteller who rides a Harley to work. The French journalist Hervé Vaudoit, who has written admiringly about Raoult over the years, once asked him why he'd taken to dressing this way. Raoult replied, "Because it pisses them off."

In the weeks since SARS-CoV-2, the virus that causes Covid-19, spread throughout the world, his disdain for respectable opinion, and for the "Parisian marquesses" who are its representatives, has endeared him to a large segment of the French population. According to one survey, by late March, Raoult had become one of France's most popular "political personalities," with particular appeal on the populist extremes. Votives bearing his image were being sold in Marseille, and on some evenings, at 8 p.m., a battalion of municipal garbage trucks assembled on the roadway outside his hospital, where the drivers leaned on their horns in loud and furious tribute. A hundred-foot banner, painted by a club of local soccer fans and strung up near the entrance, read, "Marseille and the world behind Prof. Raoult!!!"

Raoult has been collecting the merchandise created by his fans, and he seems to be enjoying his fame, though he claims otherwise. He is certain the drugs will vindicate him in the end; everything else is a matter of appearances. "I really do think we're in a theater," he told me. "In my play, the people who judge me as a doctor are my patients. As a scientist, it's my colleagues. And time."

A few weeks ago, I spoke, from the recommended distance, to a man named Jacques Cohen. He was seated on the sidewalk outside the IHU, an angular monument of concrete and glass about a mile and a half from Marseille's old port. Cohen had his back against a pylon and his wrists on his knees, at the edge of a group of perhaps 60 people. By their unworried proximity to one another — they were standing around in a loose group, as people used to, waiting to enter the hospital through a side door — they were identifiable as the unfortunates who already knew they were positive. I had selected Cohen as my interlocutor under the guidance of a nearby nurse. He was not coughing or sneezing; he wore a mask. "In any case, we're all going to get it," the nurse said.

I crouched on the pavement and asked Cohen, who is 76, how he was feeling. For the past two days, he had been taking hydroxychloroquine and azithromycin. "It's getting better," Cohen said through his mask. He looked ashen but optimistic. His fever had fallen, and he had begun to regain his sense of taste. I noted that there was some debate about the efficacy of the treatment. "There's no 'believing' or 'not believing,'" Cohen replied. "We *know* it's effective!"

Hydroxychloroquine and azithromycin are well characterized, well tolerated and widely prescribed medications. Azithromycin was developed 40 years ago in the former Yugoslavia and is today the second-most commonly prescribed antibiotic in the United States.

Hydroxychloroquine, along with its more toxic analog chloroquine, was for several decades the most commonly prescribed antimalarial drug in the world. Today it is widely used to treat rheumatoid arthritis and lupus. All three molecules are included on the World Health Organization's Model List of Essential Medicines, a compilation of "the most efficacious, safe and cost-effective medicines for priority conditions."

Raoult knows the drugs well. From the start of his career, he has experimented extensively with drug repositioning, in which medicines that have been approved for use against one disease are repurposed as treatments for others. Hundreds and hundreds of molecules have already been approved for human use by the Food and Drug Administration. Hidden among these, Raoult contends, are various unanticipated cures. "You test everything," Raoult told me. "You stop pondering; you just look and see if, by chance, something works. And what you find by chance, it'll knock you on your derrière." Antidepressants and antihypertensives have been shown to have antiviral properties; lovastatin, which is prescribed to lower cholesterol levels, has been found to be effective, at least in mice, against plague. In a 2018 paper, Raoult and a team of researchers reported that azithromycin showed strong activity in cells infected with the Zika virus.

Raoult spent the first decade of his life in Dakar, in what was then French Senegal, where his father, a military doctor, was posted. To ward off malaria, he was given chloroquine. "I took it all the time when I was a kid," he told me. In the 1990s, in an early repurposing experiment, he tested the effect of hydroxychloroquine on a frequently fatal condition known as Q fever, which is caused by an intracellular bacterium. Like viruses, intracellular bacteria multiply within the cells of their hosts; Raoult found that hydroxychloroquine, by reducing acidity within the host cells, slowed bacterial growth. He began treating Q fever with a combination of hydroxychloroquine and doxycycline and later used the same drugs for Whipple's disease, another fatal condition caused by an intracellular bacterium. The combination is now considered to be a standard treatment for both diseases.

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Given the similarities between intracellular bacteria and viruses, Raoult suspected that chloroquine and hydroxychloroquine might have antiviral effects. Following the SARS outbreak in 2002, researchers found that chloroquine slowed reproduction of the SARS coronavirus in cell cultures. Raoult reviewed that evidence in a 2007 paper, concluding that chloroquine and hydroxychloroquine might be “an interesting weapon to face present and future infectious diseases worldwide.” This winter, as the spread of SARS-CoV-2 began to take on the contours of a pandemic, he surveyed the data that had begun coming out of China. An early report on chloroquine showed good results in vitro. In mid-February, another Chinese team reported that, in more than 100 patients, it had been found to have “potent activity against Covid-19.” Raoult was elated.



A nurse at the IHU handling hydroxychloroquine and azithromycin tablets. “I’m convinced that in the end, everyone will be using this treatment,” Raoult has said. Antoine d’Agata/Magnum Photos

At the time, health authorities around the world were warning that a viable treatment could be months away. The Chinese reports, however, appeared to confirm Raoult's longstanding hopes for chloroquine. A deadly virus for which no treatment existed could evidently be stopped by an inexpensive, widely studied, pre-existing molecule, and one that Raoult knew well. A more heedful scientist might have surveyed the Chinese data and begun preparations for tests of his own. Raoult did this, but he also posted a brief, jubilant video on YouTube, under the title "Coronavirus: Game Over!" Chloroquine had produced what he called "spectacular improvements" in the Chinese patients. "It's excellent news — this is probably the easiest respiratory infection to treat of all," Raoult said. "The only thing I'll tell you is, be careful: Soon the pharmacies won't have any chloroquine left!"

Raoult has spent nearly his entire life in Marseille, a famously ragged and combative city, which he loves. He named a genus of bacteria, *Massilia*, for it and has given its name or the names of its neighborhoods to numerous other species of microbe. Marseille has been a major port for more than 2,000 years and has a correspondingly rich history of disease. It was the point of entry into France for all three of the great waves of bubonic plague, beginning in the sixth century. Between 1720 and 1722, the plague killed about half of Marseille's population; one of its central neighborhoods, on the old port, is today named for the bishop who tended to the ill while the city's doctors hid in fear.

Raoult wrote his first research paper, in 1979, on a tick-borne infection sometimes known as Marseille fever. The disease was also called "benign summer fever," and more than 50 years of science said it was nonlethal. And yet one of the 41 patients in his data set had died. Before submitting the paper, Raoult, who was then a young resident, gave it to a supervising professor for review. "And he takes it," Raoult told me, "he doesn't show it to me again, and he publishes it — and he'd taken out the death. Because he didn't know how to make sense of the death." Raoult was disgusted, and the incident shaped his philosophy of scientific inquiry. "I learned that the people who wanted to follow the familiar path were prepared to cheat in order to do it," he said. In subsequent work, he demonstrated that Marseille fever was indeed fatal in almost precisely one in every 41 cases. "He was a 'follower,'" Raoult said of the professor. "And these 'followers' are all cheaters. That's what I thought. And it's still what I think."

He is, fundamentally, a contrarian. In Raoult's view, little of consequence has been accomplished by researchers who endorse the habitual tools and theories of their age. "I've spent my life being 'against,'" he told me. "I tell young scientists: 'You know, you don't need a brain to agree. All you need is a spinal cord.'" He is thrilled by conflict. It is a matter both of philosophy — the influence, no doubt, of the thinker he refers to admiringly as "master

Nietzsche” — and of temperament. “He loves to know that things are roiling around him,” one of his lab technicians told me; he sets off storms and admires them as they roll out over the land. His peers shake their heads at this behavior but grant him a grudging respect. “You can’t knock him down,” said Mark Pallen, a professor of microbial genomics at the University of East Anglia. “In terms of his place in the canon, the sainthood of science, he’s pretty secure there.”

He is also interested in power and has been attentive to it from the start. In 1985 and 1986, Raoult worked at the Naval Medical Research Institute in Bethesda, Md., where he discovered the Science Citation Index. The index, a tool that can be used to measure a scientist’s influence on the basis of his or her publication history, was relatively unknown in France. Raoult looked up the researchers reputed to be the best in Marseille. “It was really the emperor wears no clothes,” he said. “These people didn’t publish. There was one who hadn’t written a paper in 10 years.” In Raoult’s view, French science was a duchy of appearances, connections and self-reverence. “It was people saying” — he mimed the drone of an aristocrat — “ ‘Oh, him, yes, he’s very good.’ And this reputation, you don’t know what it’s based on, but it’s not the *truth*.”

For decades, Raoult has boasted of his prodigious rates of publication and citation, which, as objective statistics, he considers to be the best measure of his worth as a researcher. Biomedical researchers in France write or contribute to perhaps 10 scientific papers every year and a few hundred in the course of a career. Raoult’s name sits atop several thousand; in each of the past eight years, he has produced more than 100. In 2020, he has already published at least 54.

Raoult is reputed to be an indefatigable worker, but he also achieves his extreme rate of publication by attaching his name to nearly every paper that comes out of his institute. Though the practice is not unheard-of, it is unusual. “Even to just read those papers would take up a large percentage of anyone’s time,” Pallen told me. “For someone like me to actually go through them carefully, critique them, make a substantial intellectual contribution — I think that would be practically impossible.”

With few exceptions, the department heads at the IHU have worked under Raoult for their entire careers, some for more than 30 years. It is an “ancestral system,” “familial” and “clanlike,” said Michel Drancourt, a clinician who is Raoult’s longest-serving collaborator. Raoult is, without question, the patriarch, and he is in some respects reputed to be benevolent. The IHU spends a great deal of money on scholarships and research grants for students from the developing world, for instance, and Raoult is known to be accessible to young researchers in a way that distinguishes him from other high-powered scientists. He

is also known for berating his subordinates. While visiting the IHU, I watched a young researcher emerge from Raoult's office in tears and rush into the arms of her friends, who were evidently accustomed to this. "When he's not happy about something, he'll let you know," one of them told me. A 2017 employee letter of complaint, which was followed by an investigation of the IHU, described the "screaming," "insults" and "psychological bullying" of a "leadership of another era." Along the entryway to Raoult's institute, there's a line from Horace: *Exegi monumentum aere perennius*, "I have crafted a monument more lasting than bronze."

In recent years, Raoult has amused himself, it seems, by staking out tendentious scientific claims, sometimes in territories that are well beyond the scope of his expertise. He is skeptical, for instance, of the utility of mathematical modeling in the realm of epidemiology. The same logic has led him to conclude that climate modelers are no more than "soothsayers" for our "scientistic era" and that their dire predictions are mostly just an attempt to expiate our intense but irrational feelings of guilt.

He is also dismissive of the alarmism that is the default position among specialists of infectious disease. He doubted, initially, that SARS-CoV-2 would spread beyond China, or that it might be a terrible problem if it did. On Jan. 20, Chinese scientists confirmed that infections were being transmitted from patient to patient, and President Xi Jinping, in his first public comments about the coronavirus, declared that all possible measures would have to be taken to contain the outbreak. The World Health Organization announced an emergency meeting. The following day, in Marseille, Raoult posted a video to his institute's YouTube channel. He faced his offscreen interviewer with weary eyes, sighed and said, "You know, the world has gone crazy." Every year, he said, there are probably 600 or 700 people who die from coronavirus infections in France and thousands more from other respiratory illnesses. "The fact that people have died from a coronavirus in China, I don't feel like it means much of anything for me," he said. "I don't know, maybe people don't have anything to do, so they've gone looking in China for something to be scared about."

Raoult's most recent book, "Epidemics: Real Dangers and False Alerts," was published in late March, by which time the W.H.O. had reported more than 330,000 confirmed cases of Covid-19 worldwide and more than 14,500 deaths. "This anguish over epidemics," he writes, "is completely untethered from the reality of deaths from infectious diseases."

By the standards of molecular biology, real-time polymerase chain reaction, the technology most commonly used to test for SARS-CoV-2, is not extravagantly complex. But it depends upon collection swabs, thermocycling machines, chemical reagents and nucleotide probes and primers, and if any one of these components is in insufficient supply, the tests cannot be

run. Beginning in January, when the SARS-CoV-2 genome was first published, the IHU bought or borrowed as much of all these as possible, spending a half million euros on new machines alone. Whatever Raoult's reservations about the virus, he did not intend to miss the opportunity to study it, and perhaps to win the race to find a treatment. His institute receives most of its funding from public sources — Raoult was given 130 million euros to build it — but it effectively controls its own budget, and Raoult, as the founding director, has near-complete control of what goes on inside its walls. “He can essentially say, ‘Hold on, I want to turn the bedroom and the dining room into a kitchen,’” Drancourt said.

Nearly 800 people work at the institute. In early March, as coronavirus patients began arriving, almost all the staff members turned their efforts to SARS-CoV-2. Raoult obtained authorization to begin a small clinical trial of hydroxychloroquine. Because viral respiratory infections often lead to secondary bacterial infections, however, Raoult wanted to test a supplementary antibiotic in some patients; he chose azithromycin, which he had previously tested against Zika. “If you're going to choose one, you might as well choose one that's been shown to be active against a virus,” said Bernard La Scola, who runs the biosafety lab at the IHU.

Hydroxychloroquine is believed to inhibit viral reproduction in infected cells by raising their pH, as in Q fever and Whipple's disease; the antiviral mechanism of azithromycin has not been explained. But what works works. If we relied only upon medications with precisely established mechanisms, a number of popular drugs — acetaminophen, for instance, the active ingredient in Tylenol — would not be in use. I asked Raoult if the idea to test the drugs together had emerged from discussions with his team. “It was me,” he told me. “Don't kid yourself.”

Swabbing a patient at the IHU in Marseille to test for SARS-CoV-2. After Raoult declared that the hospital would test and treat anyone, winding lines appeared outside its entrance. Antoine d'Agata/Magnum Photos

Testing had been scheduled to run for two weeks per patient, but after only six days, the results were so favorable that Raoult decided to end the trial and publish. “Usually, we’d take time to write, to make corrections, to consider, to go over things 50 times,” said Philippe Gautret, the department head who was the first listed author on the paper. “In this case, we were working with a sense of real urgency. Because we thought we had to get the word out, because, maybe, we’d found a way to make things better.”

Others might have proceeded with more caution or perhaps waited to confirm these results with a larger, more rigorous trial. Raoult likes to think of himself as a doctor first, however, with a moral obligation to treat his patients that supersedes any desire to produce reliable data. “We’re not going to tell someone, ‘Listen, today’s not your lucky day, you’re getting the placebo, you’re going to be dying,’” he told me. He believes it to be unnecessary, in addition to being unethical, to run randomized controlled trials, or R.C.T.s, of treatments for deadly infectious diseases. If these have become the accepted standard in biomedical research, Raoult contends, it is only because they appeal to statisticians “who have never seen a patient.” He refers to these scientists disdainfully as “methodologists.”

Raoult’s paper included results for 36 patients. Fourteen were treated with hydroxychloroquine sulfate; six were treated with a combination of hydroxychloroquine sulfate and azithromycin; and 16 served as controls. On Day 6 of the trial, 14 of the 16 control patients still tested positive for the virus. Patients receiving hydroxychloroquine fared markedly better, with only six of 14 testing positive on Day 6. Most encouraging, though, all six patients treated with a combination of hydroxychloroquine and azithromycin were found to be rid of the virus.

Several prominent French doctors cautioned that the results would have to be confirmed and warned of possible side effects. The French health minister deemed the trial promising but called for more testing. Raoult had already begun assembling data for a larger study, but he dismissed the need for anything particularly vast or lengthy. Like other critics of the R.C.T., he likes to point out that a number of self-evidently useful developments in the realm of human health have never been validated by such rigorous tests. This observation has come to be known as the parachute paradigm: We tend to accept the claim that parachutes reduce injury among people who leap from airplanes, but this effect has never been proved in a randomized study that compares an experimental parachute group to an unlucky parachuteless control. “It’s like Didier says,” Drancourt told me. “If you don’t have something that’s visible in 10 patients, or 30, it’s useless. It’s not of any consequence.” An effective treatment for a potentially lethal infectious disease will be visible to the naked eye.

On March 16, a Long Island attorney and blockchain enthusiast named Gregory Rigano appeared on Laura Ingraham’s nightly show on Fox News, “The Ingraham Angle.” Ingraham introduced the segment by asking: “What if there’s already a cheap and widely available medication, that’s on the market, to treat the virus? Well, according to a new study, there is such a drug. It’s called chloroquine.” Rigano, who at the time was falsely presenting himself as an adviser to Stanford Medical School, had recently self-published an acclamatory report on the potential of chloroquine, “An Effective Treatment for Coronavirus (Covid-19),” as a Google Doc formatted to resemble a scientific publication. It had begun to circulate in right-wing media and also in Silicon Valley; Elon Musk tweeted a link to it. Raoult saw it and noticed the attention it was receiving online. Another researcher might have found this sort of publication irresponsible and dangerous. Raoult began corresponding with Rigano and his co-author, James Todaro, an ophthalmologist and Bitcoin investor. Raoult authorized them to share his results before they had been published.

On air, Rigano announced that a researcher in the south of France, “one of the most eminent infectious-disease specialists in the whole world,” was about to publish the results of a major clinical study. “Within a matter of six days, the patients taking hydroxychloroquine tested negative for coronavirus, for Covid-19,” Rigano said. (He made no mention of azithromycin.) “We have a strong reason to believe that a preventative dose of hydroxychloroquine is going to prevent the virus from attaching to the body, and just get rid of it completely,” he added. “That’s a game changer,” Ingraham said.

In the coming days, Ingraham questioned both Anthony Fauci, the director of the National Institute of Allergy and Infectious Diseases and a member of President Trump's pandemic task force, and Alex M. Azar II, the secretary of health and human services, about the drug. Sean Hannity began promoting it as a cure for Covid-19. "Let's put it this way," he said on his radio show. "If I had it — personally, I am speaking only for Sean Hannity — I would be all over this." Rigano appeared on Tucker Carlson's show and claimed that Raoult's study had shown hydroxychloroquine to have a "100 percent cure rate against coronavirus." According to Todaro, Raoult had sent him a copy of his study and allowed him to post it on Twitter that day, two days before the preprint release. "I suspect he gave us permission because he knew it was the fastest way to disseminate the trial results," Todaro told me. (Rigano did not respond to requests for comment.) Later, Raoult himself appeared on "Dr. Oz," the talk show hosted by the celebrity doctor Mehmet Oz, a frequent Fox News guest who has promoted hydroxychloroquine. "I believe that ideas and theories are epidemic," Raoult once wrote. "When they're good, they take root."

Trump began hyping hydroxychloroquine on March 19, at a White House news conference with his coronavirus task force. "I think it's going to be very exciting," Trump said. "I think it could be a game changer and maybe not. And maybe not. But I think it could be, based on what I see, it could be a game changer. Very powerful." He suggested, inaccurately, that the F.D.A. had approved the drug for use against Covid-19. He made no mention of azithromycin. Commissioner Stephen M. Hahn of the F.D.A. gently corrected him later and said that a large clinical trial would be the appropriate way to evaluate the therapeutic value of the drug.

Still, because chloroquine and hydroxychloroquine are available for use in other conditions, doctors were able to provide Covid-19 patients with "off-label" treatment if they believed it would provide a benefit. Shortages of the drugs were reported beginning in mid-March. The F.D.A., under what appears to have been strong pressure from the Trump administration, issued an emergency-use authorization for chloroquine phosphate and hydroxychloroquine sulfate, giving doctors access to tens of millions of doses of the drugs from the Strategic National Stockpile. Unusually, the C.D.C., at what was reportedly Trump's direct urging, issued Covid-19 prescription guidelines for the drugs based upon unattributed clinical anecdotes. (The guidelines were later withdrawn.) A top government biomedical official was removed from his post, he has claimed, for having resisted political pressure to fund "potentially dangerous drugs," including hydroxychloroquine.

There is much about Raoult that might make him, and by extension his proposed treatment, appealing to a man like Trump. He is an iconoclast with funny hair; he thinks almost everyone else is stupid, especially those who are typically regarded as smart; he is beloved by the angry and conspiracy-minded; his self-congratulation is more or less unceasing. Raoult and I spoke several days after the emergency-use authorization was signed. He said he hadn't heard about it and seemed surprised, but he also said that Trump had impressed him with his intuition on hydroxychloroquine. "He's not so dumb," he said, laughing. Raoult classified Trump's psychology as that of an "entrepreneur," by way of contrast with that of a "politician." "Entrepreneurs are people who know how to decide, who know how to take risks," he said. "And at a certain point, to decide is to take a risk. Every decision is a risk."

The French waited far too long, in his estimation, to approve the use of hydroxychloroquine in Covid-19 patients. The authorization came only after Raoult announced in the press that he would continue, "in accordance with the Hippocratic oath" and effectively in defiance of the government, to treat patients with his combination therapy. "I'm convinced that in the end, everyone will be using this treatment," Raoult told *Le Parisien*. "It's just a matter of time before people agree to eat their hats."

The dynamics of a crisis are not especially conducive to reliable science. In October 1985, in the terrible early years of the AIDS epidemic, a group of French doctors, joined by the French minister of social affairs, held a news conference to announce to the world that they had discovered what looked like a cure. The drug was cyclosporine, an inexpensive immunosuppressant that had until then been used in organ transplants to prevent the rejection of new tissue. In AIDS patients, cyclosporine had the paradoxical effect of increasing white-blood-cell counts; patients underwent a "spectacular improvement," one researcher said. The announcement was based upon results from only two patients, however, and these patients had begun treatment only one week earlier. The scientists were widely criticized at the time for flouting the norms of biomedical research to report such limited data. "Given the strength of our hypotheses," they responded, "we believe that, ethically, we could not continue to keep our results a secret just to respect the usual laws of scientific conduct."

"Like Raoult, they felt very strongly about what they said," said Jean-Michel Molina, who directs the infectious-disease departments at two public hospitals in Paris. "They felt that they had found a cure." Shortly after the announcement, one of the two patients died, and it was revealed that a third patient had died before the news conference; he had been

excluded from the reported results because his case was considered too grave to reverse. Within weeks, the remaining patient's white-blood-cell count had fallen to its previous level. Experimentation with cyclosporine soon stopped.

Like many doctors, Molina viewed Raoult's study with skepticism, but he was also curious to see if his proposed treatment regimen might in fact work. He tested hydroxychloroquine and azithromycin in 11 of his own patients. "We had severe patients, and we wanted to try something," Molina told me. Within five days, one had died, and two others had been transferred out of his service to intensive care. In another patient, the treatment was suspended after the onset of cardiac issues, a known side effect of the drugs. Eight of the 10 surviving patients still tested positive for SARS-CoV-2 at the conclusion of the study period. Raoult's data had come from patients with mild or early cases of the disease, when viral loads are lower, and I asked Molina if his patients had not been too sick to benefit from the treatment. "If there is antiviral activity, you should be able to see it," he said. "You know, you may say, 'It's too late, you're not going to see the clinical benefit.' But at least you should see the antiviral activity. If it's an antiviral."

The front entrance of IHU Méditerranée Infection is closed and patients are directed to the back to test for the virus.

Antoine d'Agata/Magnum Photos

Raoult's study had measured only viral load. It offered no data on clinical outcomes, and it was not clear if the patients' actual symptoms had improved or indeed whether the patients lived or died. At the outset, 26 patients were assigned to receive hydroxychloroquine, six more than the 20 who appeared in the final results. The six additional patients had been "lost in follow-up," the authors wrote, "because of early cessation of treatment." The reasons given were concerning. One patient stopped taking the drug after developing nausea. Three patients had to be transferred out of the institute to intensive care. One patient died. (Another patient elected to leave the hospital before the end of the treatment cycle.) "So four of the 26 treated patients were actually not recovering at all," noted Elisabeth Bik, a scientific consultant who wrote a widely circulated blog post on Raoult's study. She paraphrased the sarcasm circulating on Twitter: "My results always look amazing if I leave out the patients who died."

The report was also riddled with discrepancies and apparent errors. Its selection criteria called for participants above the age of 12, but three of the control subjects were younger than this. The control patients were drawn not only from the IHU but also from hospitals in two other cities, where the standard of care and the testing protocols may have differed. Fourteen of 16 control patients were reported to have tested positive for the virus at the conclusion of the study on Day 6. In fact, according to the initial report, for five of those 14, no data was collected that day. One of the six patients who received hydroxychloroquine and azithromycin and was recorded as "virologically cured" at Day 6 was found, in the end, to be carrying the virus two days later.

This apparent sloppiness was unsurprising to many of those who have tracked Raoult's work in the past. A prominent French microbiologist told me that, in terms of publication, Raoult's reputation among scientists has been "long gone" for some time. "In private," the researcher wrote to me, "everybody agrees on the low reliability/reproducibility of most of the papers coming out of his lab." (He asked to speak anonymously so as not to anger Raoult, whom he knows.) In 2018, after damning evaluations, Raoult's principal laboratory groups were stripped of their association with two of France's top public research institutions. Raoult was found to have produced an extraordinary number of publications but few of great quality. "It's very easy to publish [expletive] when you know how publishing works," said Karine Lacombe, a professor of medicine in Paris who has recently been among Raoult's more outspoken critics.

Beyond its apparent errors and omissions, the study's design — its small size, its flawed control, the unrandomized assignment of patients to the treatment and control groups — was widely viewed to render its results meaningless. Fauci repeatedly called its results “anecdotal”; the biostatistician who analyzed the paper on behalf of the French government's coronavirus advisory committee wrote that it was “impossible to interpret the effect described therein as being attributable to treatment with hydroxychloroquine.”

Large, well-controlled randomized trials are by no means the only way to arrive at useful scientific insights. Their utility is that they enhance statistical signals such that, amid the noise of human variability and random chance, even the faint effect of some new treatment can be detected. The prime statistical hurdle that any proposed treatment for Covid-19 will have to overcome — one that is delicate for even Raoult's critics to make note of, amid the sorrow and fear of this pandemic — is that the signal is likely to be very faint, because the disease is, in the end, rarely fatal. Nearly everyone survives; an effective treatment will save the life of the one or so patients in every hundred who would not have lived without it. “You know, people sometimes say, ‘If the patient gets better, that's because of the drug, and if they get worse, it's because of the virus,’” Molina told me. “And of course that's not true. And that's why you need to do a well-conducted, randomized, placebo-controlled study if you want to show anything.” It is possible that hydroxychloroquine and azithromycin are an effective treatment for Covid-19. But Raoult's study showed, at best, that 20 people who would almost certainly have survived without any treatment at all also survived for six days while taking the drugs Raoult prescribed.

“If you haven't done this stuff, you can look at a report of people responding to such a treatment and figure that the answer is here — right here, and anyone who doesn't see it must have some ulterior motives,” Derek Lowe, a longtime pharmaceutical researcher, wrote for *Science Translational Medicine* last month. “But that's not how it works.” He went on: “Alzheimer's drugs, obesity drugs, cardiovascular drugs, osteoporosis drugs: Over and over, there have been what looked like positive results that evaporated on closer inspection. After you've experienced this a few times, you take the lesson to heart that the only way to be sure about these things is to run sufficiently powered controlled trials. No shortcuts, no gut feelings — just data.”

“**I've invented 10** or so treatments in my life,” Raoult told me. “Half of them are prescribed all over the world. I've never done a double-blind study in my life, never. Never! Never done anything randomized, either.” He noted, with some satisfaction, that the criticism was more intense than he had anticipated. “Honestly, I couldn't have imagined that it would set off a frenzy like this,” he said, leaning back in his office chair and gesturing at the storm he

had created in the world outside. “When you tell the story, it’s extremely straightforward, no? It’s subject, verb, complement: You detect a disease; there’s a drug that’s cheap, whose safety we know all about because there’s two billion people who take it; we prescribe it, and it changes what it changes. It might not be a miracle product, but it’s better than doing nothing, no?”

His subordinates defended the study as the best work they could do under the circumstances and the fastest way to alert the world to the possibility of a treatment. The use of off-site controls was not ideal, for example, but it was the only option if they wanted to move fast. “Of course it’s a methodological weakness,” Gautret, the first author, told me. “But we made do with what we had.” As for the six patients “lost in follow-up,” even if it had been possible to collect data from them, it would have been nonsensical to include most of them in their report. Their aim was “to treat people in the early stages of the disease, when it’s not yet serious,” Gautret said. “We know that in acute viral diseases, the earlier you treat, the better your chances of success. It makes no sense to include people who are at the edge of death in the study. We’re not claiming to be able to treat people who are nearly dead.” Another small study, in 80 patients, likewise showed better results for patients with mild forms of the disease.

In Marseille, Raoult told me he would be releasing a third study, this one of 1,000 patients, the following week. Initial results were published in mid-April. Raoult had treated 1,061 patients with a combination of hydroxychloroquine and azithromycin. The study was neither controlled nor randomized; at the time of the preprint release, eight patients had died, and five remained hospitalized, while 46 in total experienced a “poor clinical outcome.” The findings were summarized as “98.7 percent of patients cured so far.” The therapy constituted a “safe and efficient treatment for Covid-19,” the authors wrote.

Other scientists disagreed with this characterization of the results. “The cure rate is almost identical to what’s been described about the natural course of the disease,” the virologist Christine Rouzioux told French radio. Lacombe called Raoult’s conclusions “magical thinking,” adding: “I very honestly think he hasn’t shown anything at all.” It was soon discovered, too, that the second and third studies had been conducted without approval from a state ethics board. In an initial version of the third paper, Raoult wrote that he had conducted a “retrospective study on a cohort of patients receiving standard treatment following a research protocol previously registered.” He provided a reference to the protocol that had been approved for the first trial. But that protocol included hydroxychloroquine alone and not azithromycin; Raoult never received approval to systematically test a combination of the drugs.

The French medical regulatory agency, the A.N.S.M., sent Raoult a request for evidence of the second study's "legal status" in mid-April. Later in the month, the French Medical Council issued a statement, widely assumed to be directed at Raoult, reminding its members that "the endangerment of patients" by exposure to "treatments that have not been scientifically validated" could be cause for immediate suspension. Raoult responded on Twitter, where he now has a half million followers, that the council's threat was "obviously" not applicable to his case. In a statement on the A.N.S.M.'s inquiry, the IHU insisted that the study did not involve experimentation because "no procedure beyond the standard of care" — which, at the IHU, was hydroxychloroquine and azithromycin — had been employed.

Raoult had by then begun to lose his composure. He accused Lacombe of being a shill for the pharmaceutical industry; his fans sent her death threats. On Twitter, he called Bik, the consultant who wrote critically about the first study, a "witch hunter" and called a study that she tweeted — one of several published in April and May that seemed to suggest that Raoult's treatment regimen was ineffectual or even harmful — "fake news." The authors of another such study were accused of "scientific fraud." "My detractors are children!" Raoult told an interviewer. The world's attention has drifted to new studies of other drugs; Raoult has taken to attacking those studies for their methodological weaknesses.

The results of his initial trial have yet to be replicated. "I think what he secretly hopes is that no one will ever be able to show anything," Molina told me. "That all the trials conducted on hydroxychloroquine will not be able to even reach a conclusion of no efficacy." In recent weeks, Raoult has in fact tempered his claims about the virtues of his treatment regimen. The published, peer-reviewed version of the final study noted that another two patients had died, bringing the total to 10. Where the earlier version called the drugs "safe and efficient," they were now described merely as "safe."

He has shown flickers of what appears to be doubt. In one interview, Raoult quoted Camus, from the fatalistic coda of "The Stranger," hoping that "on the day of my execution there should be a huge crowd of spectators, and that they should greet me with howls of hatred."

"I don't trust popularity," he told the interviewer. "When too many people think you're wonderful, you should start to wonder." His initial YouTube video, "Coronavirus: Game Over!" has also been renamed. The new language is more measured, and in place of the exclamation point there now stands a question mark.