Chloroquine, Past and Present

**By**[**Derek Lowe**](https://blogs.sciencemag.org/pipeline/about-derek-lowe)**20 March, 2020**

Now that chloroquine is in the news everywhere, I thought it might be interesting to have a closer look at the compound. The first part of this post will be chemistry-heavy, further down we’ll get into the pharmacology and medical uses.



Chloroquine’s fame is as an antimalarial drug, and the history of antimalarials starts of course with [**quinine**](https://en.wikipedia.org/wiki/Quinine) (at right). That’s the active compound in cinchona bark, whose medicinal properties had long been known among the natives of South America in the tropical parts of the Andes – the Incas and the people(s) that the Incas absorbed into their empire. It doesn’t seem to have been used by them as a malaria treatment *per se*, but rather was known as a treatment for shivering, brought on by either low temperatures or by malaria itself. The Spanish conquerors introduced it into Europe in the 1600s. The study of cinchona bark and its extracts is a key part of the history of medicinal chemistry as a science – the pure compound was extracted in 1820 by Caventou and Pelletier, and the development of [**Perkin’s mauve**](https://en.wikipedia.org/wiki/Mauveine) was an attempt by Perkin himself to synthesize quinine. From a chemical standpoint, that work was doomed – no way, no how, was he going to make quinine – but the purple dye he did produce made him wealthy, famous, and kick-started the synthetic dyestuffs industry and industrial organic chemistry in general. Quinine itself wasn’t synthesized until 1944, a wartime effort by Woodward and von Doering, and there has never been a synthesis that can compete with extraction from the bark.



The search for quinine alternatives started off early, not least because the natural product itself was first a monopoly of the Spanish crown and later (via horticultural espionage similar to what happened with rubber production), a market sewn up by the Dutch through plantations in Indonesia. In 1891, Paul Ehrlich himself found that **[methylene blue](https://en.wikipedia.org/wiki/Methylene_blue)** (at right, synthetic dyestuffs, showing their stuff) was actually an antimalarial compound, although it wasn’t really effective enough to take over from quinine itself. Besides, at the doses needed, it tended to turn people (or at least various parts of them) blue. This is what you get when you start a pharmaceutical industry out of a pigments-and-dyes one. As another example, the first sulfa drug, **[Prontosil](https://en.wikipedia.org/wiki/Prontosil)**, tended to permanently turn people red; it was only later discovered that the red dye part was just structural baggage and all the activity was in the little sulfonamide on the side.



One of Bayer’s students, Wilhelm Röhl, was working at Bayer and started a program to test the company’s synthetic compounds for malarial activity and to make analogs around the active ones. That led in 1931 to quinacrine (at right), also known as **[mepacrine](https://en.wikipedia.org/wiki/Mepacrine)** or by its old trade name of Atabrine. You can see the methylene blue roots in its structure, although this one isn’t blue, it’s yellow, and also had a noticeable patient-staining effect.  It’s quite effective as an antimalarial and was used in huge quantities during the Second World War, but it has serious side effects. Not only will it turn you yellow, it can lead to psychological effects (depression and psychosis), seizures, permanent tinnitus and balance problems, and more. Other newer antimalarials such as **[mefloquine](https://en.wikipedia.org/wiki/Mefloquine)** (Lariam) have the same problems.



And so does **[chloroquine](https://en.wikipedia.org/wiki/Chloroquine)**, at right. That one was [**synthesized in 1934**](https://en.wikipedia.org/wiki/Mefloquine) by Hans Andersag at Bayer, and the initial evaluation of the drug by Bayer marked it down as too toxic for human use. This was later considered a [**major mistake**](https://www.cabdirect.org/cabdirect/abstract/19632901383) (the “resochin error”, using the drug’s German trade name), as it became a major antimalarial drug after World War II. It was considered a major advance in that it had strong antimalarial activity and didn’t actually make people change into various rainbow colors. You can see how this one came from quinacrine, just chopping off that third ring, which also gets rid of the colorful visible-light absorption properties. And it’s also getting back a bit closer to quinine, as a substituted quinoline with aminoalkyl group up at the 4 position. But it still can lead to depression and other effects. **[Hydroxychloroquine](https://en.wikipedia.org/wiki/Hydroxychloroquine)** came along in the 1950s, and just has an extra OH group coming off of one of those N-ethyls over at the end of the chain; it’s quite similar to chloroquine itself.

You might wonder how an antiparasitical drug might do that, but the problem is that the mode of action of all these drugs against malaria parasites is still being argued over. And there are almost certainly several modes of action at work, which will go on to have different effects in different human tissues, etc. Both chloroquine and hydroxychloroquine are used off-label for rheumatoid arthritis and for lupus, but [**how they work**](https://www.ncbi.nlm.nih.gov/pubmed/32034323) in these areas is another shoulder-shrugger, and there are [**side effects**](https://www.ncbi.nlm.nih.gov/pubmed/31277749) in [**the eye**](https://en.wikipedia.org/wiki/Chloroquine_retinopathy). It’s been suggested as an adjunct in some cancer therapy regimes, but there are [**problems there**](https://www.ncbi.nlm.nih.gov/pubmed/23288916), too, in the kidney.

So if you see someone confidently explaining just how chloroquine exerts whatever antiviral activity it may have, feel free to go read something else. No one’s sure yet. Viruses certainly have fewer moving parts than plasmodia do, so it might be easier to figure out what’s going on, but anyone who’s done “target ID” will tell you to settle in for some work. There are all sorts of suggestions, some of which are recycled from antimalarial hypotheses. One that I find particularly amusing, for personal reasons, is the idea of complexing zinc ions. I say that because over 20 years ago, I was on a project targeting a particular phosphatase enzyme (I know, I know, it was as doomed as all the other phosphatase work from that era. . .) Our lead compound was pretty similar to chloroquine, which is interesting because I was working for Bayer at the time – there were still plenty of such structures from way back in the compound collection. Unfortunately, none of the analogs we made were active in the slightest, so I did what I should have done right at the start and ordered up some of the original powder sample for more stringent analysis. Sending it out for elemental analysis and checking all the metallic-element boxes revealed that it was about 40% zinc by weight, and a zinc-free sample was, you guessed it, about as active as corn starch. So yeah, I can at least believe that these things complex zinc, for what that’s worth.

And so to today. As I said yesterday, I find the reports of chloroquine/hydroxychloroquine activity against the coronovirus very interesting, but preliminary. There has as yet been no well-controlled trial, and unfortunately the effects seen are still the sort of thing that can look exciting but disappear when you look closely. I mean that. It happens all the time – ask anyone else who does drug research for a living. If this drug isn’t useful, then sending hundreds of millions of people out to swallow all of it that they can find will be a massive waste of time and money, and will actively harm people besides. This is not a benign compound; it should only be taken when you have a solid expectation of benefit, and (saying it again), we don’t yet have that. Better trials are cranking up right now: please, wait for those. The generic drug companies (Teva and Mylan, I’ve seen so far, and there’s [**this**](https://twitter.com/AndrewE_Dunn/status/1241032671222009856?s=20)) that are cranking up production are doing the prudent thing – if this reads out well, we’ll need a lot of it. But we’ll need to give it to people who are in bad shape from the viral infection, too, remember that, and I fear that a lot of people around the world are just starting to take it now in hopes of a prophylactic effect, which is (saying it again) a bad idea.