

A Tale of Two Drugs: Wheat Mold, Hippies and Headaches



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An interesting best-of-times-worst-of-times story related to migraine treatment can be found in a humble wheat mold, called ergot.

Early last century pharmaceutical companies got interested in ergot and took two dramatically different roads in their attempt to develop drugs based on the effects of the mold. One road led to the development of a drug with great social effect, seemed to work for everybody, made very little money and was eventually deemed illegal. Ironically, the other drug remained legal, made a great deal of money and had highly variable efficacy. You may have taken one and possibly both of these drugs in your lifetime.

Like many good stories, this story starts in the Middle Ages when it was noted that ergot-infected wheat caused a poisoning that was called St. Anthony's Fire. In humans, two frightening effects resulted from the poisoning. The first was that it caused psychotic behavior, including rather vivid hallucinations. The second was that it caused gangrene, sometimes leading to loss of limbs, fingers or toes. Possibly the burning sensation and the resulting darkened, burned-like appearance of gangrenous fingers and toes led to the "fire" in the name St. Anthony's Fire.

If nothing else, effects of this nature in humans are pharmaceutically interesting and sure enough last century pharmaceutical companies got involved and tried to develop drugs based on the observed effects of ergot poisoning.



A bicycle trip written,
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The first road was taken by a young chemist named Dr. Albert Hofmann at the Swiss pharmaceutical company Sandoz. Believe it or not, Dr. Hofmann had been working on the gastric juices of snails (who even knew snails had anything as sophisticated as gastric juices?) before he turned his attention to experimenting with ergotamine, one of the primary compounds in ergot mold and as it turns out, a precursor of lysergic acid (LS) which itself was a precursor to LSD.

Dr. Hofmann's accidental ingestion of LSD and his very colorful bike ride through the streets of Basel makes fun reading¹ and viewing² as does an encounter with his unfortunate landlady whom he imagines to be, "a malevolent, insidious witch with a colored mask."

As we know, LSD never became a money-making blockbuster drug for Sandoz. However, it certainly did have a significant impact on the counter culture that blossomed and arguably changed the world (at least momentarily) in the 1960's. Around then the drug was declared illegal in the US and other countries.

The second road that pharmaceutical companies embarked on was motivated by the observation that ergot poisoning could lead to gangrene. This terrible effect turned out to be the result of the strong vasoconstrictive effects of ergotamine. At this point the story continues via an interesting and fortuitous encounter. That encounter happened only a quarter of a century ago in Europe at meetings of the so-called Serotonin Club between Dr. Pramond Saxena, who was studying the vasoconstrictive effects of ergotamine in migraine and a pharmacologist called Dr. Patrick Humphrey.



The dark coloration
shows ergot infection
on wheat

What Dr. Hoffmann was for Sandoz, Dr. Humphrey was for the British drug company Glaxo – a young scientist experimenting with chemistry that showed interesting biological effects. In 1984, Dr. Humphrey had synthesized a new chemical compound called GR43175 that showed powerful vasoconstrictive effects. In fact, when put into perspective with Dr. Saxena's work in migraine it acted like a "clean ergotamine". GR43175 inspired Glaxo to develop a drug for

migraine that did not have as many of the undesirable side-effects of ergotamine. That drug is now called sumatriptan – the first in a very large class of triptan-like compounds for migraine that would eventually bloom into a dozen different brands of pills, sprays and injectables and earn tens of billions of dollars worldwide.



Developing sumatriptan was not easy. Steve Donoghue, PhD, VP Clinical for Curelator Headache led the original phase 3 clinical trials of sumatriptan for Glaxo and remembers, “We needed a large clinical trial to show that oral sumatriptan was more effective than aspirin/metoclopramide.”

As the first – and only – drug developed and approved for migraine at that time, sumatriptan enjoyed substantial success, despite the fact that it had limited efficacy.

A recent review of pharmaceutical claims reported approximately 50% of patients do not even refill their initial triptan prescription³.

This is likely due to a combination of variable efficacy and adverse side effects in some individuals. In contrast, the effects of LSD are similar (and potent) in most people. Apart from their shared history, how can LSD be almost universal in its effects while the triptans (and drugs for migraine in general) display such a high degree of variability among individuals?

We think we have an answer (or a hypothesis). In reviewing the trigger and protector maps from initial Curelator Headache users, almost all migraineurs seem to have unique profiles. In other words, everybody has different triggers and protectors. If everybody is different in migraine, then it is reasonable to expect each individual to respond differently to treatments – regardless if they are hippies or not.

References:

¹LSD – *My Problem Child*, Albert Hofmann: 1980 McGraw-Hill

²A Bicycle Trip. A beautiful animated video here: <https://vimeo.com/7198391>

³Katic *et al*, *Adherence to Acute Migraine Medication: What Does It Mean, Why Does It Matter?* Headache. 2010; 50 (1):117

For a more detailed scientific explanation of drug development in migraine please see:

The History and Pharmacology of Ergotamine and Dihydroergotamine (Silberstein, S. and Hargreaves, RJ pages 52-65)

Ergots – Therapy (Dahlhof, C. and Goadsby, PJ, pages 66-82)

Both these chapters in Diener HC (ed): *Drug Treatment of Migraine and Other Headaches*. Monogr. Clin. Neurosci. Basel, Karger, 2000, Vol 17,