Engineering the sexual revolution

Chemical engineers have a lot to answer for – including the Summer of Love. **Claudia Flavell-While** explains

REFINING, reactor design, bulk plastics – the kind of world-changing developments featured thus far in this series include many of the stereotypical activities one would imagine chemical engineers to be involved in.

But the influence of chemical engineering reaches much further. How many would have suspected that the work of chemical engineers could have contributed directly to feminism and women's liberation, the swinging 60s and the sexual revolution?

It's an easily-forgotten fact, because the people in question have often been conveniently mislabelled as "chemists", but two of the key people responsible for developing the contraceptive pill were in fact chemical engineers.

They are George Rosenkranz, who in the early 1950s was research director at the Mexican chemicals company Syntex, and research student Luis Miramontes. Working with chemist Carl Djerassi, in 1951 they synthesised a substance they called norethindrone – the progesterone that was to be used in one of the first two combined oral contraceptive pills, and is still used by millions of women around the world, every day.

This is the story of how they developed it.

mavericks and renegades

The idea of a contraceptive pill based on hormones was first proposed in 1921 by the Austrian physiologist Ludwig Haberlandt. However, identifying, synthesising and correctly dosing the right hormones was not straightforward – not to mention the social resistances that would have to be overcome. At the time, research on contraceptives was illegal in many countries and even where it wasn't, established medical science largely refused to participate in this 'disreputable' area of research.

> *"no one initially realised that progesterone, especially when combined with oestrogen, was an effective contraceptive"*

During the course of the 1930s it became clear that oestrogen and progesterone had a role in preventing ovulation. But all hormones at the time had to be extracted from animal sources, a laborious process which made any hormone-based treatments horrendously expensive.

Enter Russell Marker, professor of organic chemistry at Pennsylvania State College and a real maverick of the field – much to the disdain of some colleagues, he didn't even have a PhD to his name. However, Marker did succeed in revolutionising the progesterone production process by synthesising progesterone from sapogenins, natural steroids found in Mexican yams. Marker developed a process for turning diogenin, a kind of sapogenin, into progesterone via a five-step process. Until his research became known in the mid-1940s, progesterone was prepared in a laborious process from animal glands, which limited the quantities available and kept prices sky-high. Moreover all of the relevant patents were held by European companies, giving them a competitive stranglehold over US-based research. Marker's process brought the price down by two thirds straight away and imploded the European hormone cartel, and the price fell from anywhere between $80–1000/g to less than $2/g. A new company – Syntex – was formed in Mexico to commercialise the process.

educated guesswork

Within a year, Marker left the company over a commercial disagreement, and it fell to the Hungarian Jewish emigrant George Rosenkranz – a chemical engineering graduate from the Technische Hochschule Zurich who'd fled the war to Cuba and later Mexico – to recreate Marker's process and re-start the large-scale production of progesterone.

Marker had not made it easy for him – the lab was a "shambles" and Marker's notes on starting materials and intermediates were all in code, so Rosenkranz had to use his own knowledge on steroids and a combination of detective work and educated guesses to recreate the progesterone production process. He succeeded. Within two months, Syntex's progesterone production was back on track and production soon reached levels never known before.

winning the cortisone race

Syntex first gained international recognition by being the first company to develop an industrially-viable synthesis process for cortisone, another steroid which attracted huge interest as a treatment for rheumatoid arthritis.

Syntex chemist Carl Djerassi writes in his autobiography, *This man's pill*: "Until 1951, the only source of cortisone was through an extraordinarily complex process of 36 different chemical transformations starting from animal bile acids – for many years, the longest and most complicated synthesis of any chemical on an industrial scale. Now that cortisone had emerged as a wonder drug, however, such a process looked less like a *tour de force* and more like a bottleneck." The race for cortisone captured public interest so much it's been compared to the space race, and Syntex was up against many much larger and better-funded rivals in North America. When Syntex beat the competition, the country was ecstatic.

Ironically, it took only a few months before

Gregory Pincus, John Hammond and Min-Chueh Chang, biologists at the Worcester Foundation for Experimental Biology in Massachusetts, who drove the development of the contraceptive pill

Syntex' prized process was obsolete, thanks to a biochemical fermentation developed by Upjohn that shortened the process to a single step. Luckily for Syntex, Upjohn's process relied on progesterone as a raw material, so the company was certainly not out of pocket.

high-altitude chemical cookery

Working with Rosenkranz were Carl Djerassi, another European refugee of Jewish ancestry who'd fled his native Austria and Luis Miramontes, a 26-year-old student from Universidad Nacional Autónoma de México, working on his chemical engineering PhD.

Djerassi and Rosenkranz returned their attention to progesterone. Together with Miramontes, they set out to synthesise a progesterone steroid that would combine two previously observed effects: that replacing the carbon 19 atom with hydrogen would greatly increase the compound's activity, while adding an acetylene group to position 17 would allow it to survive absorption through the digestive tract.

It fell to Miramontes to do most of the practical work, and so, on 15 October 1951, Miramontes completed the synthesis of 19-nor-17α-ethynyltestosterone or, for short 'norethindrone', which turned out to be the first oral contraceptive to be synthesised.

"Lecture audiences are always intrigued when I display a slide showing (Miramontes') carefully-dated and hand-written lab protocol of the very last step in that synthesis," he added. Most of the intrigue centres on the choice of solvent used in the final step, adding the acetylene to impart oral activity: the Syntex team used toluene as a solvent instead of benzene, the industry standard in what Djerassi calls "those pre-oncophobic years". Benzene was not only a carcinogen (though this was not known at the time), but its low boiling point made it unsuitable for the 2.4 km high altitude of Mexico City. "This was the type of high altitude chemical cookery that most gringos working in the fancy sea-level laboratories of Harvard or Merck never even had to consider," Djerassi says.

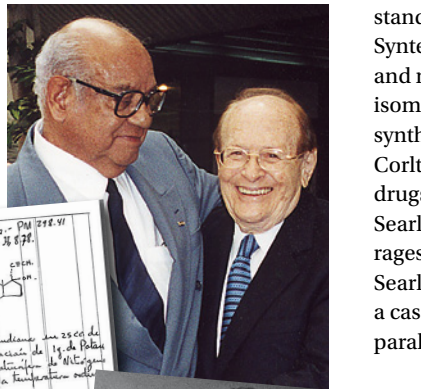
The substance was as good as the team had hoped, proving to be the most active oral progestational hormone of its time.

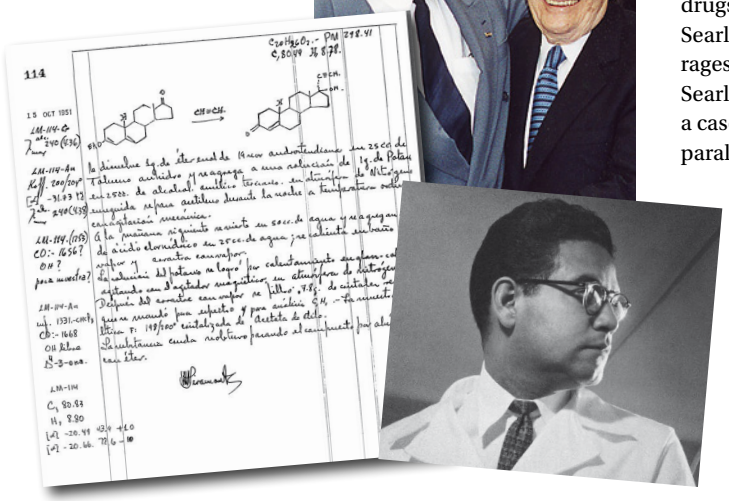
the pill that nobody wanted

Not that anyone thought of using it as a contraceptive, at least to begin with. The main use of progesterone at the time was to treat certain menstrual disorders and infertility. No one initially realised that progesterone, especially when combined with oestrogen, was an effective contraceptive – and even when they did, fear of religiously-motivated boycotts caused companies to veer away from the drug. Rosenkranz recalled: "I went around Europe and the world offering the contraceptive, but nobody wanted it."

In the end it was two women, Margaret Sanger and Katharine Dexter McCormick – both passionate campaigners for the contraceptive pill and women's rights – funding Gregory Pincus and Min-Chueh Chang, two independent-minded biologists at the Worcester Foundation for Experimental Biology in Massachusetts, who drove the development of the contraceptive pill.

They tested a range of steroids for efficacy, and settled on two stand-out versions: Syntex' norethindrone, and norethynodrel, an isomer of norethindrone synthesised by Frank Corlton at the Chicago drugs manufacturer GD Searle. Controversy still rages about whether Searle's progesterone is a case of independent parallel research, or whether their work was led and inspired by the Mexican team's – Corlton would argue the former, Djerassi would point out that his team published their patents almost two years ahead of their North American rival, thus proving it was the latter.





(Clockwise from right) , Miramontes and Rosenkranz in 2001, Luis Miramontes and the hand-written lab protocol detailing the final synthesis step

Ultimately, both would make it to market as the first combined oral contraceptive pills, though Searle ultimately launched two years earlier. Indeed, the pill has just celebrated its 50th birthday: it was on 9 May 1960 that the Food and Drug Administration first licensed it for contraceptive use.

Mexicans still take a huge amount of pride from the fact that it was their researchers, in a country normally regarded as a quiet backwater in the world of cutting edge science, who were the first to synthesise progesterone for the contraceptive pill, and the Syntex researchers involved in the development have received just about every scientific honour Mexico has to bestow.

sex and sustainability

The impact and importance of the contraceptive pill can hardly be overstated. While it did cause some social upset initially, it was a huge success from the outset. Today, over 100m women worldwide take the pill every day.

Women's liberation owes a huge debt to the pill. The sexual revolution would have been impossible without a method of contraception that was under the woman's control and divorced from the sex act. Effective family planning meant there were far fewer unwanted pregnancies and a sharp drop in risky abortions and in health problems due to constant pregnancies. Moreover, being able to plan pregnancies finally enabled women to have careers and work towards the equality of the sexes.

Gender equality and sex without fear weren't all of it though: the runaway success of the pill preceded a sharp decline in the birth rate in countries where the pill was available and affordable.

One might argue that this has made the pill the greatest ever force for sustainability there ever was – and chemical engineers were at the heart of this development. **tce**

Next month: Thomas Midgeley – climate killer or energy saver?