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# Chance, serendipity and antiepileptic drugs

MEDISINSK HISTORIE

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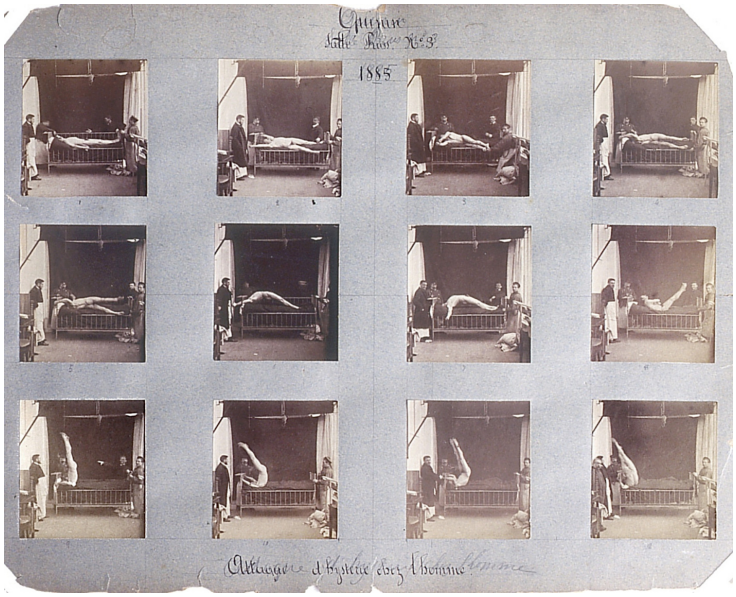
We like to believe that progress in the field of medicine is achieved through rational and scientific developments. This is not always the case. Many of our most frequently used drugs were discovered by pure chance, among them several antiepileptics.




*"Attaque d'hysterie chez l'homme" – photo series from 1885 featuring a patient at La Salpêtrière hospital in Paris. Photo: Albert Londe*

Many significant advances in the field of medicine have been based on mere coincidences,

such as Alexander Fleming's discovery of penicillin in 1928. This is only one of many examples of drugs that were discovered by pure chance, for example when drugs are found to be effective against something completely different to what they were intended for (1–3). This is also the case in epileptology.

## Bromide as an anaphrodisiac

In the 19th century, sexual activity, particularly excessive masturbation, was considered to be one of the most important causes of epilepsy. In 1857, Sir Charles Locock, obstetrician to Queen Victoria, reported dramatic seizure improvements in 18 women who suffered from "hysterical epilepsy" (most probably catamenial epilepsy) after they had received potassium bromide to quell their sexual appetite.

Towards the end of the 19th century, the National Hospital in London used almost 2 tonnes of bromide per year (4). Potassium bromide was often added to bread dough. In Norway, patients at Oslo University Hospital's National Centre for Epilepsy were given bread with potassium bromide additives as late as in 1960 (5).

Unfortunately, there were significant side effects associated with potassium bromide, often referred to as bromism: sedation, mental dullness, dribbling, ataxia and acne ("bromoderma"). The fact that patients had their libido quelled in addition to experiencing an improvement in their seizures, was seen as evidence that the sex hypothesis was correct.

## Sleeping medication with an antiepileptic effect

In 1912, phenobarbital had recently appeared on the market as a sleeping medicine branded as Luminal. At the time, a young German psychiatrist from Freiburg, Alfred Hauptmann, was living on the floor above patients who suffered from epilepsy and psychiatric disorders. They were exceedingly noisy at night, so he decided to give them phenobarbital so that he himself would be able to sleep. To his great surprise he found that not only did the patients sleep better – many no longer had epileptic seizures (6).

Even though he published his findings, phenobarbital did not become a drug of first choice against epilepsy until around 1920, perhaps because his article was published in German (7). It was not until 70 years later, in 1979, that the most important molecular mechanism behind the drug's seizure-inhibiting effect was identified – it lengthens the opening of the chloride channel in the $GABA_A$-receptor.

Even though phenobarbital undoubtedly works well against generalised tonic-clonic seizures, its use has gradually decreased in recent years, mainly due to its unfavourable side effect profile. However, the drug is cheap, and its long half-life means it is effective even if taken only once a day. In a global perspective, phenobarbital is still an important antiepileptic drug, particularly in developing countries (8), and it features on the World Health Organisation's List of Essential Medicines (9).

## Continued development of antipsychotic drugs

Following the introduction of the antipsychotic drug chlorpromazine in the early 1950s, eager attempts were made to find further psychoactive substances with a more favourable side effect profile. By retaining the tricyclic structure and making some small changes to the molecule, both tricyclic antidepressants and carbamazepine were developed.

Carbamazepine was synthesised in 1953 but its efficacy against psychosis and depression was disappointing. On the other hand, it was found – somewhat surprisingly – that the drug worked well against trigeminal neuralgia. The drug's antiepileptic properties were discovered by chance a few years later (7). While chlorpromazine and tricyclic antidepressants lower the seizure threshold, carbamazepine has the opposite effect. Similarly-structured substances can thus have completely opposite effects on the central nervous system.

Carbamazepine is now one of the most frequently used antiepileptic drugs, particularly for focal epilepsies. None of the newer antiepileptics have convincingly demonstrated a better seizure-inhibiting effect than carbamazepine. The disadvantages are some rare idiosyncratic side effects and the drug's enzyme inducing properties, which cause frequent pharmacokinetic interactions.

## Solvents as antiepileptics

The antiepileptic properties of valproic acid came as a big surprise. This simple short-chain fatty acid had been used as a solvent for more than 80 years when a small pharmaceutical company in Grenoble in 1962 decided to use it for this very purpose as they were testing a number of substances on rodents in their search for new antiepileptic drugs. Because all the substances proved to be pharmacologically active, the Meunier brothers decided to test the solvent on its own. By doing so, they found that it had remarkably good antiepileptic properties (10).

Valproate was launched on the market for the first time in 1967 and was soon widely adopted, particularly in Europe. Strangely, it took several years before it was licensed in the USA. Wicked tongues would have it that this was due to it not having been developed in the States. (The National Institutes of Health, an American research institution, abbreviates to NIH. This abbreviation was now read as "not invented here") (7).

*The first stage of epilepsy – paralysis and convulsion. Etching after a drawing by Paul Richer in his "Etudes cliniques sur la grande hystérie ou hystéro-épilepsie" from 1885. Photo: Science Photo Library*

Today valproate is a drug of first choice for generalised forms of epilepsy. It has a number of pharmacodynamic effects and is also used for bipolar disorder and migraine. It can modulate energy and hormone metabolism, and considering its enzyme inhibiting effect, it is likely to also have a number of other metabolic effects (10, 11). The drug's disadvantages are its side effects, particularly weight gain, tremors and endocrine disruptions. Its potential for harming an unborn foetus makes the drug unsuitable for women who wish to conceive (12).

## Antifolates

In the 1960s and 70s there was a theory that the seizure-inhibiting effect of the two most frequently used antiepileptic drugs at the time, phenobarbital and phenytoin, was due to their lowering of folate levels. Lamotrigine emerged as a result of the race for a new antiepileptic drug with antifolate properties. Animal testing and later clinical trials showed that the substance had very good antiepileptic properties – despite its very limited effect on folates (13). It was not until several years later that the drug's antiepileptic effect was found to be mainly due to blocking of sodium channels.

Today, lamotrigine is considered a broad-spectrum antiepileptic drug with a relatively favourable side effect profile. Due to its positive psychotropic properties, the drug is also used against mild depression.

## Antidiabetic or antiepileptic?

Topiramate, which is entirely different to other antiepileptic drugs, was also discovered by chance. The search for a new antidiabetic drug was hoped to deliver a substance that would block gluconeogenesis by inhibiting the fructose-1,6-diphosphatase enzyme.

It was a great disappointment that topiramate had only limited hypoglycaemic effect. However, the drug demonstrated very good antiepileptic properties in animal models. It has later been shown that the drug has an impact on several protein complexes, which probably explains its antiepileptic effect. These include proteins that form part of sodium channels, the $GABA_A$-receptor and the AMPA/kainate receptor.

Today there is no doubt that the drug has a good seizure-reducing effect (14), but its use is somewhat limited due to its side effects, particularly its neuropsychiatric side effects. By yet another chance event, it was also discovered that the drug may be useful in migraine prophylaxis (7).

## Antispastic, antiepiletic or analgesic?

Gabapentin and pregabalin were both developed as GABA analogues. The chemical basis for their development was an attempt to attach GABA to lipophilic components, which would enable the molecules to go through the blood-brain-barrier with greater ease. The idea was for this to quell seizures by strengthening GABAergic inhibition.

However, it turned out that the drugs had no effect at all on the GABA level. They had a structural likeness to GABA but no functional likeness (15). They did however have antiepileptic properties, probably by binding to a subunit ($\alpha 2\delta$) in voltage-gated calcium channels. The binding influences the presynaptic release of transmitters, such as glutamate (16).

Gabapentin was first assumed to have an antispastic effect due to its structural similarity to baclofen, but its antispastic effect proved to be limited (17). However, patients who were taking gabapentin or pregabalin reported pain relief, and since then these drugs have been in much wider use against neuropathic pain than against epilepsy. Pregabalin has also been demonstrated to be highly efficacious against generalised anxiety (18).

## Antidementia or antiepileptic?

Piracetam is a nootropic which in high doses has a degree of efficacy against cortical myoclonus. Because the drug was reputed to improve cognitive functions, it was used by students before exams. However, studies showed that the drug does not in fact improve cognition beyond a mere placebo effect. This was a great disappointment to UCB Pharma, that owns the product. The company therefore started to modify the piracetam molecule in the hope that they might find a new antidementia drug. This is how levetiracetam came to be.


*Bromine/bromide was used over a long period of time – from the 19th century to the 1960s – after it was found not only to quell the patient's libido, but to also have a beneficial effect on epileptic seizures. Apothecary bottle from the Wehmann Collection (of medical antiquities), Berlin. Photo: Akg-images /NTB scanpix*

However, traditional animal epilepsy models indicated that levetiracetam gave no improvement in cognitive functions, and that it had no particular seizure-reducing effect. Initially, the company therefore showed little interest in the substance. But after Wolfgang Löscher in Hannover in 1992 tested it on animals with seizures induced by electric kindling, which is a more stringent model than traditional testing, and demonstrated very good antiepileptic effects, the company's interest reawakened (7).

Since then, levetiracetam has been very widely used against epilepsy – and has become a significant source of revenue for the company. It is currently considered to be extremely useful as a broad-spectrum antiepileptic drug. It was only in 2004 that the presumed molecular mechanism behind the drug's seizure-inhibiting effect was identified: it bound to a synaptic vesicle protein (SV2A). Exactly how this binding reduces the neuronal excitability is however still unclear (19). Several acetam derivatives are currently being developed, and brivaracetam is already on the market in Norway.

## Modern neuroscience emerges

Recent decades have seen enormous progress in the neurosciences, and these advances have led to the discovery of new antiepileptics with new mechanisms of action. This has often happened by pure chance.

In the 1930s, the Americans Merritt & Putnam developed animal epilepsy models. Phenytoin, which was introduced in 1938, was a result of systematic testing of a series of substances in these models. The substances had an aromatic ring which was chemically

related to phenobarbital (20). The discovery that the antiepileptic effect was not necessarily linked to sedation, was a big step forward for humans who suffer from epilepsy. It was a surprise that the molecular mechanism behind phenytoin's seizure-inhibiting effect was demonstrated not to be linked to GABAergic inhibition, which was the case with phenobarbital, but to a blocking of sodium channels in the neuronal cell membrane (21).

The anti-absence drug ethosuximide, with calcium blocking properties, was also discovered at this stage due to its structural similarity to phenytoin (22). It has been said that ethosuximide could trigger generalised tonic-clonic seizures while phenytoin can boost the tendency to absences (23). The fact that structurally similar substances can have opposite central nervous effects, is also well illustrated by the two neurotransmitters GABA and glutamate, which despite their structural similarities have inhibitory and facilitatory effects respectively on impulse transmission in the brain.

## Chemical design

The era of rational chemical design commenced once the signal substances in the central nervous system were discovered in the 1960s and 70s (24). Several decades of painstaking translational research laid the groundwork for this development.

In 1990 vigabatrin emerged as the first antiepileptic drug that was designed with a specific mechanism of action in mind, namely to inhibit the breakdown of GABA by inhibiting the enzyme GABA aminotransferase. The substance is now little used by adults due to retinal toxicity with irreversible visual field impairment (25). Vigabatrin had good seizure-reducing effects in cases of focal epilepsy, but surprisingly in generalised epilepsies it often had the opposite effect (23).

We have gradually learnt that neuromodulatory substances can have a variety of different effects, both synergistic and antagonistic (26). These may alter depending on minor changes in the molecule.

## The antiepileptic drugs of the future

Currently the biggest challenge to the pharmacological treatment of epilepsy is to find medications that not only have a palliative, seizure-reducing effect, but that also have disease-modifying and preferably antiepileptogenic properties, i.e. they may prevent epilepsy from developing after, for example, a head injury. For that to happen, we need to acquire better insight into the mechanisms underlying epilepsy and pharmacological resistance.

We have yet to find valid biomarkers that typify and demarcate the dysfunctional cerebral cell network in epilepsy. It is probable that epilepsy is the result of a cascade of changes in this network, and in the future, we may need to develop drugs with multisite effects (27).

There is still a possibility that efficacious and safe antiepileptics may be discovered by pure chance. Vigilance and inquisitiveness are important qualities if we are to push science forwards in our search for new drugs with hitherto unknown mechanisms of action. It is unlikely that the antiepileptic properties of valproate would ever have been discovered had no-one imagined that a simple solvent might be efficacious.

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