

The rise of the pharmaceutical industry and the evolution of dominance of synthetic drugs

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Science

The 18th century, ie. the last century before the development of the pharmaceutical industry (and homeopathy), was the golden era of phytotherapy. However, from the 19th century onwards, dynamically developing chemistry and more precisely, organic chemistry, resulted in the isolation of an ever-growing number of natural substances, their semi-synthetic transformations and the total syntheses of organic compounds. In addition, many inorganic compounds have been prepared, too. Rudimentary experiments of their effects on the human body have already begun.

In the meantime, the process of the discovery and introduction of new drugs of herbal and animal origin continued, and even when the intensity of introduction of new phytopharmaceuticals decreased around the end of the 19th century, the age of the therapeutic use of animal organs ('organotherapy') started and continued for a couple of decades.

Although the number of synthetic, active substances in Hungary significantly increased in Hungarian Pharmacopoeias from the 1st edition (1871) to the 4th edition (1934) and the number of phytotherapeutics and substances of animal origin decreased to a lesser extent, these changes did not mirror reality at all. In reality there had been a surge of new active substances, called unofficial drugs (ie. not included in the Pharmacopoeia), to the market, as well as a flood of secret drugs (drugs with secret composition).

As a result, pharmacopoeias became clearly unable to properly regulate the pharmaceutical market and drug therapy, which gave rise to the introduction of mandatory drug registration in Hungary in 1933.

The patent system

It is very important to note, that synthetic medicinal compounds were protected in Hungary from 1895 to 1994 by patents on their manufacturing routes instead of the medicinal compounds themselves. Nevertheless, phytopharmaceuticals have not been protected by patents at all, making it less favourable to invest in their development.

Pharmacies

The above changes had no significant impact on the everyday life of classic, compounding pharmacies. Of course, they started to use the new, industry-made, active substances and excipients, in addition to their usual materials and finished compounded pharmaceutical products in their traditional ways, in the laboratory of the pharmacy shop. In other words, for a couple of decades, the pharmaceutical industry focused only on the discovery and manufacturing of active substances and excipients.

The number of Hungarian pharmacies and pharmacists grew steadily up to the end of World War I. This growth could keep pace with the increasing demand of medicinal products, which was altogether not so high. Most pharmacies could make a living from compounding ten or so prescriptions a day and additionally selling cosmetics. This would be unimaginable now.

Health insurance

In the meantime, from the middle of the 19th century, health insurance started to develop and became mandatory in Hungary in 1891. Already in 1904, a total number of 633.922 people had health insurance (the most populous exception was agricultural workers). Therefore, against all shortcomings and problems, an increasing number of employees were channeled, in an organised way into the healthcare system (at least they could have been seen by a doctor now and then) and could receive reimbursed medicinal therapy.

The pharmaceutical companies

At the beginning of the 20th century the Hungarian pharmaceutical industry was still in an embryonic stage of development. Since Hungary had no significant chemical industry, pharmaceutical companies and pharmacies mostly used imported, industry-made substances. It should be noted, that this problem was characteristic for the whole period: later the relatively well-developed Hungarian pharmaceutical industry lacked a similarly well-developed chemical industry running in the background.

Industry-made isolated, semi-synthetic and synthetic substances tended to have stronger and better defined physiological effects and side effects compared to traditional phytopharmaceuticals. Consequently, their single doses were smaller, which made them eligible for formulation in modern dosage forms, such as tablets and injections, where it was of high importance to use well-defined, clean active substances in small quantities. (It is to be noted, that the 2nd edition of Hungarian Pharmacopoeia in 1902 contained only 2 pastilles, despite the fact that many more eligible substances had been available, but the 4th edition of the Pharmacopoeia in 1934 contained 25 tablets).

Pharmacies manufactured tablets and injections, too, but these manufacturing processes were rapidly monopolised by pharmaceutical companies. For example, the first Hungarian injection plant (ERI factory) had originated in a community pharmacy. These companies could manufacture larger batches at a lower price and deliver them to pharmacies for distribution to the public. From this time on, pharmacies gradually started to become points of distribution for finished, industry-made, pharmaceutical products. Finished, industry-made, pharmaceutical products were much more convenient for the patients, too, since they received them immediately, without waiting hours for their compounding, which might have been especially problematic in the countryside. In addition, these preparations tended to be more efficacious, because, for example, the tablet dosage form was clearly associated with the predominant use of new synthetic, active substances.

Reaction of the pharmacists

All of these developments were watched with worry by the leadership of the Hungarian Pharmacist Association, because they strongly opposed giving up compounding, which was regarded as the core of professional activity of pharmacists and the compounding fee was the basic source of revenue. They were especially worried about industry-made tablets. In response to this challenge, they created the so called NOSTRA movement (somewhat similar to the German STADA, which they used as an example), which offered locally compounded medicines, including tablets, in centrally produced, uniform packaging. These were based on centrally developed and published recipes, in addition to the pharmacopoeial ones and the pharmacies own recipes. NOSTRA published a tablet recipe book in 1935. The Hungarian Pharmacist Association published in 1940 a Formulary (another recipe book), called *Formulae Normales* or FoNo, as a weapon against what was perceived as the unjustified, harmful spreading of industry-made preparations to the pharmacies and, at the end, to the patients.

However, after a transitory success, these efforts finally, were not supported by the government, which re-edited the FoNo according to the requirements of the industry. This was the time of historic defeat of compounding pharmacy in Hungary. From then on, compounding became unambiguously secondary to industry-made preparations.

This was, of course, justified, because with historical hindsight, it is clear that pharmacies would have been unable to provide medicinal products in the necessary quality and quantity to meet the increasing demand powered by health insurance and the fact that in general more and more people entered the healthcare system and bought drugs at some point during their lives.

Taken together, contemporary pharmacy, as it is now, is the nightmare, from the point of view of the pharmacist leadership 80-90 years ago, which they wanted to avoid and featured as a tragic turn for

pharmacists and pharmacies. Our contemporary colleagues are not aware of this pre-history and look at current pharmacy as a natural state of affairs.

Scientific rationality: real values and make-believes

It should be emphasized, that the above changes have little to do with the real therapeutic value of industry-made preparations. Clinical studies and trials were not mandatory at that time, but nevertheless, they were conducted for both scientific and marketing reasons. However, their methodology was still rudimentary and their results questionable. Of course,, many isolated natural, semi-synthetic and synthetic active substances of real therapeutic value stood the test of time during these decades, in an expanding number of therapeutic fields. Though the main driving force behind the increasing use of industry-made medicines was not as much their therapeutic value, as their eligibility to be manufactured on an industrial scale, their relatively low price, easy access, strong marketing and the development of a positive image, according to which, the industrial civilisation generally and the pharmaceutical industry particularly, was omnipotent and would ultimately find the best cure for every disease.

In many cases pharmacotherapy played a more important role in everyday medical treatment than objectively justified on the basis of proven efficacy. However, there is nothing new included: most medicines in the 19th century and before had been for a placebo effect at best and many of them caused severe side effects, which gave rise to homeopathy.

The real significance or circumstance of the use of pharmacotherapy are often questionable even today, especially in the treatment of diseases in which life style plays a significant role, such as type 2. diabetes mellitus, hypertension or lipid disorders.

All in all, pharmacotherapy has been used many times in a kind of faith-based way, without knowing the real scientific-therapeutic value of the applied medicines.

With rare exceptions the use of drugs of animal origin gradually died out and that of phytotherapeutics largely lost ground. Phytotherapy, the mainstream type of therapy in the 18th century, became increasingly obsolete in the following 150 years. The language of medical writings on phytotherapy became archaic (eg. 'blood cleansing' herbs, etc.), medical interest and industrial use decreased, manufacturing of herbal preparations was shifted to smaller, financially weaker companies, not eager to invest into risky, expensive clinical studies. In addition, the patent system was also not favourable for phytotherapeutic innovations. However, phytotherapy has not disappeared. Instead, it has become a complementary type of therapy. For example, about 40% of medicinal herbs on the 18th century labels of pharmacy jars and drawers of a Hungarian town pharmacy in Székesfehérvár are used today in the form of different phytotherapeutic preparations, while 60% of them are utilised in homeopathy.

The nature of truth and complementary medicine

The first hotbed of alternative medicinal methods:

There are two kinds of truth:

- a) *Absolute or deterministic truth*, to which we are conditioned by evolution. In this case the input inevitably and definitely determines the output. In other words, the relationship between input and output, ie. action and reaction is direct and absolutely clear. Eg. one takes a high dose of poison and one dies.
- b) *Stochastic or non-deterministic truth* is, when one input produces, instead of a well-defined single output, a frequency distribution with many possible outputs. In other words, on an individual level the relationship between input and output, ie. action and reaction is not fully predictable. For example, one person can have a completely healthy life style and still develop lung cancer, which is predominantly linked to smoking. In reverse, another person can smoke for years and years and never develop lung cancer.

It is a very ancient idea to link sin and punishment. When people see a disease, they tend to perceive it as a kind of punishment and automatically start looking for a 'sin' provoking that disease.

On a statistical level, stochastic truth can be very well described and handled matematically, but an individual level, when a disease develops, people tend to see in it injustice, hidden 'sin', punishment of God, etc. This moral and psychological ambiguity is a hotbed of alternative medicinal methods.

The second hotbed of alternative medicinal methods: Doctors and pharmacists of the industrial society often regard themselves and their therapeutic tools as more rational than they actually are and neglect the importance of psychological factors. Medicine has become treadmill-like. Of course, this does not mean that psychological factors can really be neglected. It only means, that patients try to find solutions which comfort them in other directions, which objectively might be harmful or useless. Demand for complementary medicines will always be there and does not seem to fade away. It is evident, on the basis of the last 100 years or more that scientific advances have had no impact at all on the demand for alternative or complementary medicines. Consequently, we should study the reasons and characteristics of using complementary medicines in more depth, and should regulate their use as far as we can to the benefit of patients.

Conclusions

Evolution of the dominance of synthetic drugs has clearly less to do with their real therapeutic value than generally thought. However, there are societal factors playing a role in this process, which have been

undervalued, including the patent system, industrial scale finished product manufacturing, health insurance, marketing and a general belief held by the industrial society of the omnipotence of technology and science and that what is new, is usually better.

The pharmaceutical industry, of course, brought a very huge positive contribution to healthcare. But each civilisation, including the industrial civilisation, is a bubble, which tries to solve or manage its problems (in some cases generated or aggravated by itself) with its own tools. In this case, the industrial civilisation improved healthcare with industrial tools, which resulted in miraculous successes. But as all human inventions, it has limitations, too.

The present

We are living in an era when pharmaceutical industry does not, any longer, seem to be able to discover new blockbuster drugs for diseases of large, public health significance. Instead, research and development has been shifted to narrow fields (niche products) and combination therapies.

The image of the triumphal march of pharmacotherapy has disappeared. Today, more research is published on lifestyle issues, pharmacovigilance, compliance, diagnostic or therapeutic use of information technology and technologically advanced dosage forms. These might help in further rationalisation of pharmacotherapy.

The future

Many synthetic medicines are eternal or at least hold long-term value to society. Therefore, their manufacture and use will continue. Perhaps, as pharmaceutical companies originally developed from pharmacy shops or dye factories, future health service companies will evolve from current pharmaceutical companies and provide therapy-management services in addition to medicinal products, such as targeted, individually optimised drug therapies based on (pharmaco)genetic testing and special dosage forms. If, of course, the Welfare State survives.