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The Return of Ehrlich's 'Therapia magna sterilisans' and Other Ehrlich Concepts?

Series of Papers Honoring Paul Ehrlich on the Occasion of His 150th Birthday

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Abstract
On March 14th of this year, the birthday of Paul Ehrlich, the great German researcher and 'founder of chemotherapy', returned for the 150th time. Interestingly, his later colleague Emil von Behring was born one day later in 1854. Both were coworkers in Robert Koch's laboratory and became Nobel Prize laureates (for their work in immunology), making great contributions to antiinfectious treatments. Emil von Behring's approach was through the use of immunological agents, while Ehrlich favored an approach of antiinfectious treatment by chemical agents. Through an ingenious concept that was a clear continuation of his early days in research with dyes, he found the first chemotherapeutic agents. From his dye work, he had concluded the following: if there are dyes that one can use to stain cells, why not develop pharmacological agents that, like stains, also attach to a structure in the living pathogen and kill them. He gave these agents the emotionally charged name 'magic bullets'. This introductory review will initiate a series of papers on the occasion of Ehrlich's 150th birthday and the 'World Conference on Dosing of Antiinfectives: Dosing the Magic Bullets', which is going to be held in Nürnberg, Germany, from September 9 to 11, 2004 (see www.ehrlich2004.org). Apart from the conference topic, this conference will also commemorate a real science giant of the last century and yet a modest human being whom, as Robert Koch put it, 'one had to like'. This article recalls Ehrlich's ingenious concepts, including modern syphilis treatment, one-dose treatment ('therapia magna sterilisans') of *Helicobacter pylori* infections and introduction of an arsenic compound, arsenic trioxide, as well as experiments and new exciting data on Congo red, a well-known 'non-Ehrlich dye'.

Introduction

With this article, *Chemotherapy* begins a series of publications on the occasion of Paul Ehrlich's 150th birthday, which occurred on March 14 2004. Emil von Behring, another famous German specialist on infectious diseases, was born one day later in 1854. Later in their life, Ehrlich and von Behring became partners in the laboratory of Robert Koch, but they also became competitors, and so their 'friendship' had ups and downs. For a long period,

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Emil von Behring opposed Ehrlich's approach to curing infections with 'chemicals' rather than vaccines. When Ehrlich died in 1915, though, it was von Behring who held an impressive and emotional speech at the funeral service. This speech showed that von Behring had admired Ehrlich's ingenious path to chemotherapy, saying that Ehrlich was truly a 'Magister Mundi', i.e. master of the world's science. In addition, von Behring was aware that without Ehrlich, his success with the first diphtheria vaccine would not have been possible. Emil von Behring received the first Nobel Prize ever awarded in medicine alone in 1901, but Ehrlich had to wait until 1908 and then had to share it with Mechnikov. Both had had numerous nominations since the introduction of the Nobel Prize in 1901. It has been speculated and seems to be well documented in the Nobel archives [1] that had Ehrlich not died so early, he would have been given the Nobel Prize for chemistry together with his Japanese coworker Dr. Sahachiro Hata, with whom he developed 'compound 606' (arsphenamine and as trade name Salvarsan®) in 1910. That success marks the beginning of chemotherapy. Thus, there is no doubt that Paul Ehrlich is not only the founder of chemotherapy, but he actually invented that term.

In spite of the undoubted breakthrough in the treatment of syphilis, the use of Salvarsan was a matter of discussion in Germany and around the world. In spite of Ehrlich's great caution to have it used appropriately, it was misused and adverse events were inevitable. Together with the use of Salvarsan, Ehrlich also introduced the concept of the 'therapia magna sterilisans', as he called it. 'Therapia magna sterilisans' means successful treatment of an infectious disease by a single dose of that agent. Ehrlich liked to use Latin language to define his major hypotheses or theories, like the very famous one leading to the receptor concept: 'copora non agunt nisi fixata'. The hope of realizing single-dose treatment was in fact supported by Ehrlich's experiments with dyes and finally Salvarsan in animals and humans. Very soon after the beginning of Salvarsan treatment in patients, Ehrlich had to admit, though, that this concept of one large dose may not be valid for all patients.

Since then, the concept of 'therapia magna sterilisans' has been forgotten, although used in many instances without knowing. It was taken as a relic of the early times of chemotherapy, not worth thinking about it. I now report several examples from modern times and even most recent times of documented cases where 'a single dose' of an antiinfective has been used successfully in clinical studies with today's standards of clinical research. The objective of this article is to rethink the concept and to acknowledge Ehrlich's great achievements in the year of his 150th birthday.

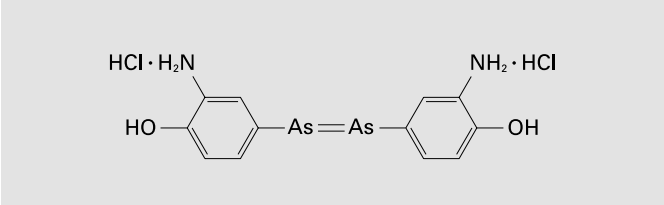

Fig. 1. Chemical structure of arsphenamine ('606', Salvarsan®).

'Therapia magna sterilisans' of Syphilis

Soon after its introduction into clinical medicine, penicillin became the standard for syphilis treatment, and Ehrlich's Salvarsan became of marginal importance. Benzathine penicillin is still successfully used today to treat syphilis [2]. That form of penicillin provides long-lasting penicillin G levels in the blood and tissues, and hence a single dose may be successful in many cases.

Of course we do not know much about the pharmacokinetics of Salvarsan, and it is not clear whether it was due to a pharmacokinetic reason that 'therapia magna sterilisans' of syphilis failed with this agent. However, it is my hypothesis that Ehrlich's Salvarsan had – among other reasons – too short a half-life to be dosed once only.

We also should not forget the fact, though, that single-dose therapy has been an aspect in the management of most common sexually transmitted diseases, such as syphilis, gonorrhea, trichomoniasis and chancroid. Of the agents used in addition to benzathine penicillin in syphilis treatment, azithromycin has such a long half-life in plasma and tissues that it has become the modern choice for syphilis treatment. A very recent study with this agent showed that – as in Ehrlich's day – one has to assess the adverse events very carefully. In fact, in their study, Rekart et al. [3] used another important concept of pharmacology, which is dosing according to weight, forming at least two dosing groups. That led to a reduction in gastrointestinal adverse events. This concept was also originally introduced and used by Ehrlich. Very early on in the use of Salvarsan therapy, Ehrlich suggested dosing according to weight and gender. An excellent review of this 'double-edged sword' of single-dose therapy has been published by Kingston and Carlin [4].

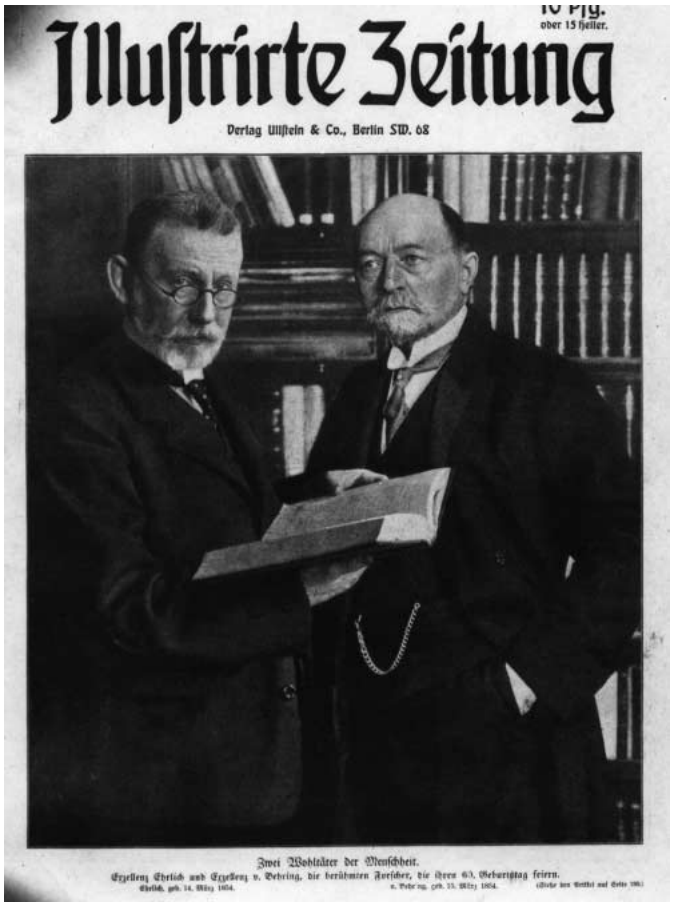

Fig. 2. One of the rare pictures where these two great German researchers, Ehrlich and von Behring, are shown together, in the newspaper the 'Illustrirte Zeitung' of Berlin (today it reads 'Illustrierte'). (Reprinted courtesy of Aventis Behring, Germany.)

'Therapia magna sterilisans' and Emergence of Resistance

Recently, Coates et al. [5], in an excellent review of modern antimicrobial treatment and its failures, shortcomings and misconceptions, suggested shorter treatment that may consequently include 'one-day' treatment. Discussion on shorter versus longer treatment to prevent resistance has very recently become a controversial topic again. With their articles, these authors may pave the way to a complete rethinking of antimicrobial chemotherapy. Along those lines, arguments have been put forth that 'dose optimization' of an antimicrobial can prevent the emergence of resistant microorganisms. This idea has great appeal, and there are good in vitro and animal data that support it [6, 7]. The animal work clearly shows that there is a relationship between the dose administered and the prevention of resistance. As Polk [8] points out, these strategies, however, would only be expected to work against organisms that become resistant by selection of resistant mutations, and would not be expected to be effective against organisms that require the acquisition of new resistant genes. However, whether the same thing happens in humans is less clear, and there are a number of reasons why dose optimization is not likely to be a very effective strategy. Foremost is that most of the species of bacteria that are increasingly resistant to chemotherapy arise not from the pathogen pool (analogous to the infected mouse thigh), but from the pool of innocent bystanders (the gastrointestinal flora of the infected mouse). In addition, the pharmacokinetics/pharmacodynamics parameters in the commensal pool, such as those in the gastrointestinal tract or the skin, are very different from pharmacokinetics/pharmacodynamics parameters based on serum concentrations, and it is unknown what the concentration-effect relationships are in these noninfected areas. These theses of Polk [8] certainly deserve discussion.

One-Day Quadruple Therapy for *Helicobacter pylori* Infection

Not too far back, the eradication of *H. pylori* involved a 3-week treatment with a not insignificant number of adverse events in these therapies with up to four drugs. Many attempts were made to shorten that treatment, and short-period treatment has been introduced. Most recently, most spectacular results were published by Lara et al. [9]. In a randomized, prospective, open-labeled equivalence trial with a parallel-group design to compare eradication rates of *H. pylori* in 160 patients, the 1-day group using four agents (524 mg of bismuth subsalicylate, 500 mg of metronidazole and 2,000 mg of amoxicillin four times a day, and 30 mg of lansoprazole twice a day) had a slightly higher eradication rate (95%) than the 7-day group (90%). Interestingly, the adverse events with, for example, 8 g of amoxicillin per day were not different between the groups, although this finding may have been hampered by the means of assessing adverse events, which was undertaken several weeks after treatment. This finding needs to be confirmed in additional trials, but for the moment it remains a most interesting finding. Other than in the case of benzathine penicillin and azithromycin, this drug combination has no component with a long half-life, suggesting that other mechanisms must underlie this finding.

Arsenic Trioxide

Although Ehrlich's arsenic compound 606 (Salvarsan) was an organic arsenic with arsenic captured chemically, it was his achievement to make arsenic compounds and to render their toxicity preventable and countable. On this basis, the recent introduction of arsenic trioxide recalls Ehrlich, who made these agents usable in human medicine. Arsenic trioxide has demonstrated efficacy and safety in patients with first and subsequent relapsed or refractory acute promyelocytic leukemia, regardless of the disease-free interval. Treatment of relapsed and refractory patients with this novel therapy produces complete remission in 87 of patients and molecular remission in 83%. Studies have documented the efficacy of autologous and allogeneic transplantation as salvage therapy in relapsed and refractory acute promyelocytic leukemia [10].

Ehrlich's Dyes and Old 'Non-Ehrlich Dyes' in Modern Molecular Pharmacology and Drug Discovery

It was one of Ehrlich's great achievements to carry the concept of the use of dyes through from histology to chemotherapy. His first dye to be used was methylene blue for treatment of malaria in human patients. Although active, methylene blue did not become a 'magic bullet'. His second attempt was trypan red, which he used to treat trypanosomes, but this was only tested in animals and a few humans. Finally, Ehrlich found '606', which was not part of a synthesis of dyes but happened to be a yellow dye. These three colors are used in the logo of the conference commemorating his 150th birthday [11]. A very recent report from Harvard Medical School [12] showed that the dye Congo red has been successfully tested to rid mice of a neurogenerative condition similar to Huntington's disease by dissolving clumps of abnormal proteins in the brain. Interestingly, these investigators used two of Ehrlich's concepts. The first is the staining of amyloid deposits in dead brain by Congo red, which led to testing of this dye as a pharmacological agent to rescue live Huntington's disease cells. Before that may successfully happen in humans, an agent must be found that acts like Congo red in the brain cells but which can – unlike Congo red – also pass the blood-brain barrier. In addition, the blood barrier was first described by one of Ehrlich's coworkers, Goldman, revealing the second aspect of this modern research related to Ehrlich's work and interest.

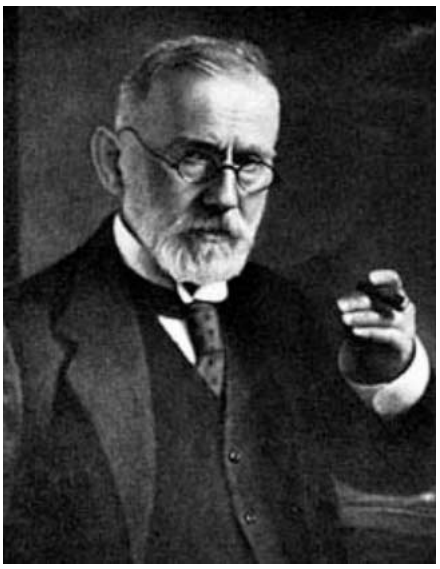

Fig. 3. Paul Ehrlich (1854–1915). The founder of chemotherapy and winner of the Nobel Prize in Medicine in 1908. (Photo reprinted courtesy of Aventis Behring, Germany.)

Fig. 4. Emil von Behring (1854–1917). Winner of the Nobel Prize in Medicine in 1901. (Photo reprinted courtesy of Aventis Behring, Germany.)

Conclusions

This very short review of Ehrlich's impact on today's scientific work shows very clearly that honoring Paul Ehrlich with this great 'World Conference on Dosing of Antiinfectives: Dosing the Magic Bullets' will review on an international level the use of modern 'magic bullets' – the least the modern chemotherapy community and this journal can do to remember a great German scientist. We are continuing Ehrlich's chemotherapy.

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