Journal of the Royal Society of Medicine
http://jrs.sagepub.com/

The introduction of 'chemotherapy' using arsphenamine – the first magic bullet

KJ Williams

J R Soc Med 2009 102: 343
DOI: 10.1258/jrsm.2009.09k036

The online version of this article can be found at:
http://jrs.sagepub.com/content/102/8/343

Published by:
SAGE
http://www.sagepublications.com

On behalf of:

The Royal Society of Medicine

Additional services and information for *Journal of the Royal Society of Medicine* can be found at:

Email Alerts: http://jrs.sagepub.com/cgi/alerts

Subscriptions: http://jrs.sagepub.com/subscriptions

Reprints: http://www.sagepub.com/journalsReprints.nav

Permissions: http://www.sagepub.com/journalsPermissions.nav

>> Version of Record - Aug 1, 2009

What is This?

Downloaded from jrs.sagepub.com at The Royal Society of Medicine Library on October 14, 2014

The introduction of 'chemotherapy' using arsphenamine – the first magic bullet

KJ Williams

5 Maplewood Road, Wilmslow, Cheshire SK9 2RY, UK

E-mail: kjwilliams510@aol.com

DECLARATIONS

Competing interests
None declared

Funding
None

Ethical approval
Not applicable

Guarantor
KJW

Contributorship
KJW is the sole contributor

Acknowledgements
The author is grateful to Tilli Tansey and Ulrich Troehler for comments on an earlier version of this commentary. Additional material for this article is available from the James Lind Library website (www.jameslindlibrary.org), where it was originally published

Paul Ehrlich and studies of the effects of dyes on infectious organisms

In the late 19th century, Paul Ehrlich (1854–1915) developed an early interest in the specific staining of tissues with dyes, first with methylene blue and then with trypan red and atoxyl. He reasoned this might allow the detection of a substance that would specifically bind to and kill microbes without harming human cells. After working initially under Robert Koch in Berlin, Ehrlich moved to his own institute in Frankfurt (Main). After it had been shown in 1905 that atoxyl, an arsenical, had some activity against trypanosomes, his chemists, led by Alfred Bertheim, synthesized a series of arsenical derivatives.

Over this period Ehrlich developed a close relationship with Professor August Laubenheimer, who had joined the pharmaceutical arm of the Meister, Lucius and Bruening dyeworks, now better known by their location (Hoechst). Ehrlich's work expanded in 1906 after he moved his laboratory into the Georg Speyer Haus, near Frankfurt, close to the dye factories. There were some partial successes, for example, compound 418 (arsenophenylglycine), which was tested clinically by the dermatologist Alfred Neisser (whose name we now associate with the gonococcus). Compound 418 also had some activity when tested in Africa against trypanosomes, which cause sleeping sickness, but it was not as powerful as atoxyl. Ehrlich was looking for an agent that could achieve sterile cultures in animals with a single dose. He coined the terms 'chemotherapy' and 'magic bullet' to characterize the processes he had in mind. He first used the term 'magic bullet' at a Harben Lecture in London in 1908,[1] although the concept (*Zauberkugel*) had appeared earlier in his writings in German.[2]

Syphilis was a scourge affecting a significant proportion of men and women in the early 20th century. Routine therapy for the disease had been with mercury, both as an ointment and internally, but this was quite toxic.[3] In 1905, Fritz Schaudinn and Erich Hoffmann identified the causative organism of syphilis – a spirochaete – which belonged to the same group of organisms as the trypanosomes. So it was that another arsenical – diamino dihydroxy arsenobenzol (arsphenamine) – was discovered, synthesized in 1907 by Alfred Bertheim, and tested on spirochaetes by Ehrlich's assistants. The two assistants who first tested it concluded that it was useless, and it was therefore put aside until Ehrlich asked his Japanese assistant, Sahashiro Hata, to repeat the experiments. Hata found that arsphenamine was superior to all the other drugs that had been tested, prompting Ehrlich's fury that the inadequate methods used by his former assistants had resulted in the delay in this discovery.[3]

Arsphenamine was known first by the number 606, as the 606th preparation tested in Ehrlich's laboratory, and subsequently by its trade name *Salvarsan* when it was marketed in 1910. Ehrlich continued to evaluate further compounds and improved upon *Salvarsan* with compound 914, *Neosalvarsan*, which was more soluble and had a lower arsenical content and appeared more active.

Dramatic effects of *Salvarsan* in patients

Salvarsan was tested in patients for the first time in the spring of 1909. Ehrlich was cautious because of the disaster that had followed Robert Koch's totally unsystematic clinical testing of his presumptive wonder drug, *Tuberculin*. Ehrlich therefore arranged for carefully recorded clinical studies to

Downloaded from jrs.sagepub.com at The Royal Society of Medicine Library on October 14, 2014

be done by a small group of doctors in Uchtspringe (Alt), Magdeburg (Schneider), Bonn (Hoffmann), St Petersburg (Iversen) and Pavia (Ascoli), giving guidance on dose and selection of patients. Later the same year, Ehrlich's friend Konrad Alt provided the first published report of the dramatic effects of *Salvarsan* in patients.[4]

> *'In total, 31 patients with progressive paralysis were treated, all of whom had previously had a definite positive Wassermann reaction (repeatedly demonstrated); 7 of them lost the [positive] reaction completely, in one it returned after 5 weeks, [but] in the others it remained negative. In a larger number, the Wassermann reaction decreased substantially, but returned to its former level after some time. Initially we had not treated patients with high doses, so some of the cases may not have responded for this reason. It seems that it was cases of less than 2 years duration of paralysis who were mostly influenced …'*

Alt recognized the need for a larger case series:

> *'The question of whether and how the clinical course of paralysis has been affected is obviously crucial. It would be premature to make a judgement in so changeable a disease on the grounds of such a small number. We have seen a rapid and noticeable improvement not only in some patients who lost the [positive] Wassermann reaction, but also in many others. Whether this was due to the treatment can only be decided after a larger test series and a longer observation period …'*
>
> *'Our treatment trials with arsenophenylglycine in patients with progressive paralysis are being extended to a larger series. One may claim already, without being overhasty, that our preliminary results support the hope that it should not be completely ruled out that, sooner or later, we will no longer be forced to confront entirely with folded arms the future course of patients with an early diagnosis of progressive paralysis. As the remissions of such patients show clearly, the paralytic process can at least be brought a standstill, even if not to a cure.'*

The year after Alt's report, Wilhelm Wechselmann's lecture to the Berlin Medical Society on 22 June was published.[5]

> *'The questions which one had naturally to ask when examining a new preparation were:*
>
> *(1) Does it have a specific effect in syphilis, and if so, does it exceed that of already known drugs;*
> *(2) Does it cure syphilis;*
> *(3) Is the eventual risk of the drug in an acceptable balance with the size of its [beneficial] effects?'*
>
> *'Concerning the first point, there can no longer be any doubt at all, even when judging with the greatest scepticism, that the new drug acts on the symptoms of syphilis in all infectious forms with a speed and thoroughness which no other drug so far known can match, even approximately. We have tried this out in 80 cases and the effects occur with the certainty of an experiment …'*
>
> *'The curative effects are so rapid that one cannot demonstrate patients because after a few days there is no longer anything to be seen on them, and they leave the hospital.'*

Still, like Konrad Alt, Wechselmann concluded optimistically but cautiously:

> *'We are aware that everything I have presented today still leaves many gaps; however, this is inevitable in such a new situation. We shall have to continue working quietly and critically in order to determine the exact indication and contraindications of the drug. However, one may safely say today that Ehrlich's genius has won a big battle in the war against syphilis. But because the path which has led to today's results has been based on firm scientific experimental foundations, we can be quietly confident that this path is the right one, and express our hope that it will lead us to final victory.'*

By the end of 1910 – the year the drug was given its trade name *Salvarsan* – some 65,000 doses had been administered to over 20,000 patients, a previously unheard of series before marketing, as was noted at the first presentation of the clinical results in Wiesbaden in 1910.[6]

Salvarsan was prepared at Hoechst in stainless steel containers by a complex chemical process with a yield just under 16%, avoiding explosions and fires due to volatile ether. It was a fine yellow powder, soluble in water, ether and glycerine, which had to be packaged under carbon dioxide in ampoules, to prevent oxidation to a toxic form. By November 1910, Hoechst was producing 12,000–14,000 ampoules per day and Ehrlich was able to offer small amounts to the many doctors who requested a supply, but only after quality controls and further tests in his laboratory. Tests were

Downloaded from jrs.sagepub.com at The Royal Society of Medicine Library on October 14, 2014

developed to assess the drug's state of oxidation and to test for its presence in the urine of patients.

McDonagh and the evaluation of *Salvarsan* in Britain

In Britain, the most substantial early experience with *Salvarsan* was obtained at the Lock Hospital, London, by James McDonagh (1881–1965), who was the outpatient surgeon at the hospital from 1909 to 1929.[7–11] The hospital had been founded in 1746 as the first voluntary hospital for venereal diseases, and was originally in a building in Grosvenor Place, near Hyde Park.[12] By McDonagh's time, male outpatients were seen in a building in Dean Street, female patients in one in Harrow Road.

McDonagh published a book about *Salvarsan* in 1912.[7] It describes the drug's history, explains its method of administration, and provides estimates of its potency against *Spirochaete pallida* (*Treponema pallidum*). McDonagh explained what the drug did and did not do and its uses and abuses, observing that, like all new remedies, it had to pass through the two stages of initial extravagant laudation and then extravagant abuse. He illustrated these with many case reports and pictures of genital and extragenital chancres, and the complications associated with syphilis.

McDonagh's book is more of a review of his extensive experience with illustrated cases rather than a numerical summary. The early chapters give an overall account of his experience, without tabulated data or numbers, written in the usual 'authoritative' style, supported by detailed case histories. Chapters are devoted to toxic reactions, neurorecurrences, fatal cases following injection and contraindications. The emphasis of the text then turns to methods of administration, effects on the syphilis test developed by August von Wassermann and the excretion of arsenic. Case histories are used to illustrate results in the primary, secondary and tertiary stages stage of syphilis, syphilis of the nervous system, congenital syphilis and then conditions other than syphilis. The book ends with a short postscript on early experience with *Neosalvarsan*.

McDonagh described some general observations that had already been made in earlier studies in Germany, including the 'immunity' to *Salvarsan* that could occur in patients already pre-treated with other arsenicals, observing that 'immunity' was more likely after intramuscular doses. Also, although *Salvarsan* eliminated parasites in the tertian form of malaria, they recurred and did not respond as well to a second course, though *Salvarsan* therapy made them more susceptible to quinine. McDonagh also recognized that *Salvarsan* was somewhat variable in action, depending on its solubility and acidity. Already some discrepancies had been observed between effects in animals and humans, and skin tests to evaluate the likelihood of reactions (as with tuberculin) were poorly predictive.

By 1912 some problems had emerged with *Salvarsan*.[7,13] In his book, McDonagh referred to Wechselmann's suggestion that dead bacteria and fungi in the distilled water caused the fever and rigors that sometimes followed administration of the drug, and he confirmed Wechselmann's 1910 observations by using re-distilled water to avoid the problems. The inflammatory condition caused by *Salvarsan* injection also made it theoretically unwise to use the drug in people with epilepsy, in case the inflammation gave rise to seizures. However McDonagh treated a case who not only recovered his memory but had no further seizures. *Salvarsan* had its most marked toxic effect on patients already suffering from meningitis or even alcohol poisoning, which was deemed to have 'weakened the tissues'. Another issue relating to the patients under evaluation was the development of concurrent conditions such as *Herpes genitalis* or chest infections. Summarizing the drug's safety profile, McDonagh stated that 'there is no drug which has not at some time or another given rise to toxic symptoms, so differently constituted in each human frame'. He considered humans to be more sensitive than animals to these effects, and that it was impossible to predict who would be affected.

McDonagh's book was important in confirming the early promise of *Salvarsan* and establishing its efficacy, which contrasted with the exorbitant claims made for several other German patent medicines at the time. This work became an important milestone in demonstrating the growing importance of the German dye industry, which produced 90% of the world's synthetic dyes, and the diversification into pharmaceuticals of firms such as Hoechst, Bayer and others. These developments had already given rise to phenol antiseptics, phenacetin, aspirin and a growing number of synthetic drugs.

Downloaded from jrs.sagepub.com at The Royal Society of Medicine Library on October 14, 2014

In addition to his book, McDonagh commented frequently on these issues in the medical literature, as it was clear that not everyone shared his views. Regarding the toxic effects of *Salvarsan* he wrote:

> *'As all of us require an unbiased opinion upon Salvarsan, it would have been better to have given a summary of the whole of the Fifth German Congress of Neurologists held last October in Frankfurt, as then we could have heard both sides. Hearing only one side leaves this side widely open to criticism. In this country more than any other we have heard so much as to what the "great" or "well-known" syphilologists think of Salvarsan. Notice that their greatness has increased since the advent of the drug, although as often as not they have never given an injection. Why an able clinician or a reader of many books should be able to judge a subject of which his experience is* nil *must be an enigma for many.'*[8]

Manufacture of arsphenamine in Britain

Recognition of the reliance on Germany for drugs was brought home dramatically two years later with the sudden outbreak of World War I, when German drugs became unavailable.[11] My research on the origins of the synthetic drug industry in England[14] showed that Burroughs Wellcome was, to the surprise of Hoechst, able to synthesize and produce arsphenamine and other synthetic drugs within weeks of the outbreak of war, when the patents of the drugs were abrogated. Although synthetic chemistry had begun on a small scale in Britain in the 1890s and Burroughs Wellcome had synthesised various alkaloids to show that they had extracted and purified the active ingredients from plants, Britain had failed to produce synthetic drugs on a large scale.[15] The British firms were many times smaller than the German dye firms and could not compete with them in producing synthetic drugs. Furthermore, Britain was also reliant on the German firms for many of the raw materials required.

Throughout the early stages of the war, great emphasis was placed upon demonstrating that the arsphenamine produced by Burroughs Wellcome, and marketed as *Kharsivan*, was as good as the German products *Salvarsan*, *Neosalvarsan* and later *Silver Salvarsan*. The recently established Medical Research Committee (MRC) had incorporated several Burroughs Wellcome staff, leaving the firm with a shortage of experience to perform assays, so the MRC became involved in the process of assay and standardization.

However, McDonagh, who had read the patents and literature, remarked that 'because they are chemically identical it does not follow that they are similar in other respects.' He pointed out that German patents were written in a way to deceive so how could British products be the same. Many of his complex arguments about incomplete linkages and side reactions confused his main point, which was that clinical data rather than animal tests of purity were needed.[14] He wrote:

> *'I am fairly of the opinion from several toxic effects I have seen following the use of the new products that the successful manufacture has not been solved and that the medical profession would be well advised to await the reports of clinicians before using the product.'*[9]

This was not the message that the MRC wanted to convey, as all they had was British and some French arsphenamine.

The MRC played a prominent role in supporting the British synthetic drug industry. Initially they focused on the manufacturing and assay controls but following the heated discussions with McDonagh they realized they needed data on clinical efficacy and safety, particularly as the Select Committee on Patent Medicines had recently challenged the many unsubstantiated reports of cures of venereal diseases.[14] The MRC appealed to members of the medical profession, who:

> *'would be performing a service of national importance, in the present emergency, by keeping accurate records of cases in which the new preparations were used, and by placing such records at the disposal of the committee for their private information and guidance. Particular stress must be laid upon the desirability of recording in every case, the name of the preparation used and the serial number applied by the manufacturer to the particular batch employed together with such details as to dosage, the precautions taken to ensure purity of the water used and finally the results of the administration, both as regards therapeutic efficacy and the presence or absence of special incidental symptoms.'*[16]

Downloaded from jrs.sagepub.com at The Royal Society of Medicine Library on October 14, 2014

One of the most important of the reports stimulated by this call was published by HC Lucey, who worked at the Royal Herbert Hospital, Woolwich. Recording his experience with 600 injections of the British arsphenamine, he concluded 'I believe *Kharsivan* to be every bit as potent as the original German preparation in the incidence of adverse reactions and the bactericidal power of the blood'.[17]

The British army in France studied *Kharsivan* (the Burroughs Wellcome trade mark for its version of arsphenamine) and *Galyl* (the Poulenc Frères version of the drug imported by the Anglo French Drug Company).[14] Collected under conditions of war, these data were not as extensive as those that seemed to have been collated earlier in Germany.[14] Although cure rates were high, estimates of adverse reactions were very variable, and valid comparisons between the French, British and German versions of arsphenamine were impossible.[14] Much as the MRC wanted to prove that British *Kharsivan* was as effective and as well tolerated as German *Salvarsan*, the data were insufficient to support confident claims – yet the MRC still stated publicly that British arsphenamine was as good as German arsphenamine.

As a result of continued controversy, the MRC set up a second *Salvarsan* Committee in 1917. Even after the war had ended, the MRC defended British arsphenamine, although they recognized privately that it was impossible to provide reliable comparative data with the German product. An annual report issued five years later argued that the Committee had assisted not only in 'meeting an immediate national need, but in founding an industry which [would] be of increasing importance to the practice of medicine'.[18]

It did indeed prove to be a turning point in the history of the pharmaceutical industry in Britain. Although Burroughs Wellcome had previously synthesized drugs, it had done so only to confirm the properties of their alkaloidal extracts. The company did not attempt to compete on a commercial scale with the huge German dye firms. In the 'needs must' situation of World War I, as others took up drug synthesis and large scale manufacture, Burroughs Wellcome shared its experience with Allen & Hanburys, Boots, Evans and British Drug Houses. Subsequent growth in experience placed Britain in a stronger position when the country next faced the prospect of war with Germany.

This had immediate benefits in 1922–1923 in the production of insulin,[19] which, although not synthetic, required elaborate control procedures for large scale manufacture. These developments were driven particularly by Francis Carr, a chemical engineer who had been involved in producing arsphenamine at Burroughs Wellcome, who moved first to Boots and then to British Drug Houses. It is often not appreciated that, as early as 1921, industry (through Carr in particular) asked the Medical Research Council to establish a system of clinical trials to test its products.[14] Though clinical trials remained unregulated, they were overseen by committees of the Medical Research Council, and subsequently by its Therapeutic Trials Committee.[19,20]

As far as the treatment of syphilis was concerned, arsenicals remained the mainstay of treatment of syphilis, later in combination with bismuth, until penicillin became widely available after World War II. Penicillin then rapidly became accepted as the treatment of choice, although penicillin treatment schedules for syphilis were not standardized until 1960.[21]

References

1 Ehrlich P. *Experimental researches on specific therapy. On immunity with special relationship between distribution and action of antigens. Harben Lecture*. London: Lewis; 1908
2 Witkop B. Paul Ehrlich and his magic bullets – revisited. Lecture given at the Paul Ehrlich Foundation, Frankfurt, 13 November 1998. See http://www.aps-pub.com/proceedings/1434/Witkop
3 Abraham JJ. Some account of the history of the treatment of syphilis. *Br J Venereal Diseases* 1948;**24**:153–61
4 Alt K. Behandlungsversuche mit Arsenophenylglyzin bei Paralytikern. *Muenchener Medizinische Wochenschrift* 1909;**56**:1457–9
5 Wechselmann W. Über die Behandlung der Syphilis mit Dioxydiamido-arseno-benzol. *Berliner Klinische Wochenschrift* 1910;**47**:1261–4
6 Baumler E. *Paul Ehrlich. Scientist for life*. New York, NY: Holmes & Meier; 1984
7 McDonagh JER. *Salvarsan in syphilis and allied diseases*. Oxford: Oxford Medical Publications; 1912
8 McDonagh JER. Some toxic effects of Salvarsan. *BMJ* 1912;**1**:272
9 McDonagh JER. The manufacture of Salvarsan products in England and France. *BMJ* 1915;**1**:697
10 McDonagh JER. The manufacture of Salvarsan products in England and France. *BMJ* 1915;**1**:742
11 McDonagh JER. The chemio-therapeutics of Mr McDonagh. *BMJ* 1916;**2**:340–1
12 Williams DI. *Short History of the London Lock Hospital and Rescue Home 1746–1906*. London: Lock Hospital; 1906
13 Yakimoff WL, Kohl-Yakimoff N. Der Einfluss von Mikroben auf die Wirkung des Salvarsan. *Muenchener Medizinische Wochenschrift* 1911;**58**:2601–4

Downloaded from jrs.sagepub.com at The Royal Society of Medicine Library on October 14, 2014

14 Williams KJ. *British pharmaceutical industry, synthetic drug manufacture and the clinical testing of novel drugs 1895–1939. PhD thesis*. Manchester: University of Manchester; 2005
15 Church RA, Tansey EM. *Burroughs, Wellcome & Co., Knowledge, Trust and Profit, and the transformation of the British pharmaceutical industry*. Lancaster: Carnegie Publishing; 2007
16 Editorial. The manufacture of Salvarsan products in England and France. *BMJ* 1915;10 April:1091
17 Lucey HC. The therapeutic and reaction effects of *Kharsivan*; a record of 600 injections. *BMJ* 1916;**1**:614–16
18 Medical Research Council. *5th Annual Report*. London; MRC; 1922
19 Cox-Maximov D. *The making of the clinical trial in Britain, 1910–1945: expertise, the state and the public. PhD thesis*. Cambridge: University of Cambridge; 1997
20 Toth B. *Clinical trials in British medicine 1848–1948, with special reference to the development of the randomised controlled trial. PhD thesis*. Bristol: University of Bristol; 1998
21 Benedek T. The 'Tuskegee Study' of syphilis: analysis of moral versus methodologic aspects. In: Reverby SM, ed. *Tuskegee's truths: rethinking the Tuskegee Syphilis Study*. Chapel Hill, NC: University of North Carolina Press; 2000. p. 213–35

Downloaded from jrs.sagepub.com at The Royal Society of Medicine Library on October 14, 2014