

# A biography of arsenic and medicine in Hong Kong and China

Arsenic trioxide has been used in traditional Chinese medicine for over 5000 years, but lost its appeal due to its toxicity. It was rediscovered in western medicine and enjoyed a renaissance from 1830 to 1930, as the first effective chemotherapy against syphilis, parasites and leukaemia. These years were also a time of political turmoil in China. The Nanking treaty (29 August 1842) turned Hong Kong into a colony, while the Xinhai Revolution (10 October 1911) gave birth to a republic of China. Arsenic returned to China and Hong Kong with the establishment of the first medical schools from 1887 to 1920. Until 1950, oral arsenic trioxide was the standard anti-leukaemic treatment in Queen Mary Hospital. The advent of alkylating chemotherapeutic agents replaced arsenic trioxide in Hong Kong and around the world. In the 1970s, however, the specific activity of arsenic trioxide against acute promyelocytic leukaemia was re-discovered during the Cultural Revolution in Harbin, China. In 1997, Hong Kong was returned to China. In the same year, arsenic trioxide returned to the world stage. Intravenous arsenic trioxide became the worldwide standard therapy for relapsed acute promyelocytic leukaemia. Oral administration of arsenic trioxide was revived in Hong Kong in 2000. This resulted in the first locally produced, registered, patented prescription drug in Hong Kong. Pending imminent manufacture, this product is poised to revolutionise acute promyelocytic leukaemia care and may hold the key to saving the lives of acute promyelocytic leukaemia patients worldwide. The remarkable journey of arsenic in the setting of medical history of China and Hong Kong is reviewed.

## Introduction

Traditional Chinese medicine (TCM) is based on the balance of the five humors (五行) and a harmony between the positive and negative (yin and yang 陰陽) forces. Hence, one substance overcomes another substance to recreate a state of equilibrium. The concept of using a controlled dose of poison to overcome an ailment (以毒攻毒) is one principle in TCM. Such poisons included natural elements (eg lead, arsenic, mercury) as well as plant and animal toxins (snakes, toad, and scorpion). The origin of TCM can be traced back to 2800 BC, with the mythical figure of Emperor *Shennong* (神農) regarded as its most ancient master. It is possible that *Shennong* refers to a clan, tribe, or guild with medical knowledge rather than an actual person.

## Arsenic and its origins in traditional Chinese medicine

The verbatim knowledge of TCM was first gathered systematically in the text *Shennong Materia Medica* (神農本草經), compiled in unified China during the Han (漢) dynasty (200 BC). Two forms of arsenic were mentioned: arsenic sulphide ( $As_4S_4$ , realgar or male yellow 雄黃) and arsenic trioxide ( $As_2O_3$ , arsenolite or *pishuang* 砒霜). Another form of yellow arsenic sulphide, orpiment or female yellow (雌黃), was also known and commonly used as correction ink on yellow paper (信口雌黃). Realgar was used for chills

and rigors, jaundice, necrosis, malignant ulcers and “various parasitic infestations” (主寒熱、鼠瘻、惡瘡、疽痔、死肌、殺百蟲毒腫). A mixture of male and female arsenic was used for “malignant growths”.<sup>1</sup>

The use of various forms of arsenic continued in TCM for the next 2000 years. Li Shi Zhen's (李時珍) *Compendium of Materia Medica* (本草綱目) from the Song (北宋) dynasty (1590 AD) listed *pishuang* as a drug with violent side-effects (砒乃大熱大毒之藥，砒霜之毒尤烈). It was supposed to be effective against toxin accumulation, obstructive symptoms, gangrene, chronic ulcers and cervical lymphadenopathy (解毒治壅、爛肉、蝕瘀腐、癩鬚). It was a drastic measure for drastic conditions (有出奇制勝的效果). Realgar and orpiment, on the other hand, were advised for such diverse conditions as cough, pains and convulsive fits (治冷痰勞嗽，心腹痛癲癩). Topical applications could be used for chronic ulcers (外用治腹脅痞塊). Both were contraindicated in anaemic conditions and chronic usage was recognised as potentially harmful (不可久服傷人).

Interestingly, the observed efficacy of TCM arsenic for chronic skin diseases, fits and cough was replicated in the West in the 19th century, where various arsenic-containing solutions (Fowler's solution, Donovan's solution, Gay's solution) were used against psoriasis, epilepsy and asthma respectively.<sup>2</sup> Arsenic trioxide continues to be listed in the Compendium for Chinese medicine up to this date. The World Health Organization

## 撫今追昔：砒霜在中國和香港的發展

砒霜（砷）被應用於中醫藥，已有過千年歷史。但因其毒性猛烈，遂被淪為偏方。但從1830到1930的一百年間，它卻在西方醫學大放異彩，成為對抗梅毒、寄生蟲，以至血癌的一線藥物。這百年亦適逢中國的政史動盪：南京條約（1842年8月29日）揭開了香港的殖民地歷史，辛亥革命（1911年10月10日）建立了共和的新中國。自1887到1920年間，中港兩地各自成立了西醫學院，而砒霜亦曾以西藥的身份重臨中國。二次大戰後，砒霜逐漸被新的化療藥物取代。而在瑪麗醫院，口服砒霜治癌也沿用至1950年而告終。不料在1970年間，在文化大革命的艱鉅日子裏，它竟奇跡地從哈爾濱捲土重來，成為對抗急性早幼粒細胞白血病（APL）近乎萬試萬靈的中藥注射劑。1997年香港回歸中國，同年砒霜注射劑亦風行全球，成為對抗APL的靈丹妙藥。到了千禧年代，香港大學復用了戰前的口服砒霜，並把它發展成本港首項專利研發及註冊處方的西藥。價錢普及，使用方便的砒霜口服劑即將在港投產，這勢將再次改變治療APL的世界潮流，及為眾多發展中國家裏無藥可用的APL病人重燃生機。本文撫今追昔，寄望前人的智慧，今得發揚光大，造福病人。

registered Chinese National Pharmacopoeia (國家藥典ISBN: 750252062, English 1997) listed 23 arsenic compounds, whose indications included lung cancer and nasopharyngeal carcinoma.<sup>2</sup> The use of arsenic in TCM declined because of its notoriety as a poison. Its alleged victims included the last royals of the Ming and Qing dynasties (明長平公主，清光緒帝). Arsenic was literally synonymous with poison (熊掌砒霜，飲鳩止渴). Currently, the use of arsenic as TCM is banned in Hong Kong.

### Arsenic's appearance and disappearance in western medicine

Similarly, in the 18th century in the West, arsenic first gained fame as a poison. *Aqua Toffana*, an arsenic trioxide solution, was the favourite death drink used by aristocrats to quietly dispatch unwanted persons (named after lady Toffa, killed in Naples in 1709). Medicinally, Thomas Wilson patented the first arsenic medication in 1771 for treating agues and malaria.<sup>2</sup> Thomas Fowler, an Edinburgh graduate of 1778, produced a 1% solution of potassium arsenite to bear his name. The original recipe (in Latin) and paper entitled "*Medical Reports on the Effects of Arsenic*" were published in 1786.<sup>3</sup> The solution gained popularity as a tonic for farm animals, improving their skin texture and preventing parasite infestations. Arsenic is still used today to treat filariasis (heartworm) in dogs, and is added to animal feeds for chicken and pigs for prevention of parasitic infestations, weight gain, and "better outlook". Fowler's solution first appeared in the London Pharmacopoeia of 1809.<sup>4</sup> In 1858, David Livingston suggested its use for trypanosomiasis in Africa. In 1865, Lissauer from

Germany gave the tonic (intended for his horses) to a woman with chronic myelogenous leukaemia (CML). This improved her anaemia, splenomegaly, and leukocytosis.<sup>5</sup> These reports did not gain much credit as arsenic was regarded as being too poisonous for use. However, it was known that mountain peasants of Styria of Austria chronically consume oral arsenic for generations as a health tonic.<sup>2</sup> In 1867, at the Royal College of Physicians of Edinburgh, Robert Craig MacLagan presented his accounts of the Styrians who "regularly spread arsenic ore on their bread".<sup>6</sup> Their urine specimens showed unequivocal presence of arsenic by the Marsh test. A rapid growth of interest in arsenic therapeutics followed.

The century from 1830s to 1930s was arsenic's golden age. It became the backbone of the fight against infections, infestations, and malignancies. Fowler's solution was the standard anti-syphilitic and anti-parasitic treatment. For European nations, syphilis and African sleeping sickness were the two obstacles to building an army and colonising Africa. A competition began between England and Germany to develop more powerful and less toxic organic arsenic compounds against spirochaetes and trypanosomes. In 1905, Harold Thomas of Liverpool used an arsenic derivative atoxyl (literally, *non-toxic*) to kill trypanosomes. Nobel laureate Robert Koch tested it in Africa and found that 2% of patients (and normal "volunteers") go blind. In 1909, Koch's protégé, Nobel laureate Paul Ehrlich and his student Sahachiro Hata (秦佐八郎) tested hundreds of compound and found that number (No.) 606 worked best. Salvarsan (literally: *arsenic that saves*) remained the "*therapia magna sterilisans*" (one shot magic bullet) for treating syphilis until the introduction of penicillin in World War II.<sup>7</sup> Meanwhile in China in 1922, Ernest Carroll Faust used arsenic compounds as a broad-spectrum anti-parasitic drug for infestations due to filaria, amoeba, and schistosomes. In 1938, Ernst Friedheim combined arsenic and its antidote Lewisite (used for arsenic gas warfare in World War I) to produce melarsoprol. Although largely replaced by other drugs, even today melarsoprol remains the last resort for advanced African sleeping illness. Finally, in haematology, in 1878, doctors from the Boston City Hospital documented the effects of arsenic trioxide on blood counts in anaemic, normal, and leukaemic individuals. Further studies in CML were undertaken by a young American haematologist Claude Forkner, a descendant of pre-revolution Scottish settlers. He took an interest in CML since his medical school dissection partner died of the disease.<sup>8</sup> Like Lissauer 66 years ago, he reported sustained control of white cell counts, anaemia and splenomegaly.<sup>9</sup> Arsenic became the first effective chemotherapy for leukaemia. It was only phased out after World War II with new treatments (alkylating chemotherapy<sup>10</sup> and radioisotope treatment<sup>11</sup>) developed during that time.

## Arsenic returned to China as western medicine

In 1828, Thomas R Colledge from Aberdeen opened China's first hospital, the Canton Poh Tsai Hospital (博濟醫院, now Second Affiliated Hospital of the Sun Yat-sen University). Under the London Missionary Society, William Lockhart from Liverpool founded hospitals in Hong Kong (1842), Shanghai (1843, now Renji hospital, 仁濟醫院) and Peking (1861, later part of Peking Union Medical College [PUMC] 北京協和醫院). After the Opium War, Hong Kong became a British colony (29 August 1842). Her first Chinese doctors, Huang Kuan (黃寬) and Sir Ho Kai (何啟), graduated from Edinburgh and Aberdeen in 1853 and 1879, respectively. In 1883, Sir Patrick Manson (Father of Tropical Medicine) arrived from Aberdeen.<sup>12</sup> He had achieved regional fame in Taiwan by performing surgery on a 19-year-old man with filariasis (elephantiasis). In his misery, the young man had attempted suicide by chronically consuming arsenic, which may have inadvertently helped to medically control his disease. In 1887, Manson saved Li Hung-chang (李鴻章) by draining his quinsy. The same year, the Hong Kong College of Medicine for Chinese was inaugurated under Manson and fellow Scotsman Sir James Cantlie. Both were renowned malaria experts and their standard malaria treatment was a combination of quinine, arsenic, opium, and mercury.<sup>13</sup> Li Hung-chang served as the College's honorary patron, till his death in 1901.<sup>12</sup> In 1892, the College's first and most famous student, Sun Yat-sen (國父孫中山, "Father of The Nation") graduated. During the last westernisation campaign (洋務運動, 1885-1894), Li convinced Empress Cixi (慈禧) to set up the navy-funded Pei Yang Medical School (北洋醫學堂 incorporated into Hebei Medical University in 1933). Li's army surgeon, Sir H McCartney from Edinburgh served as its supervisor. On Cantlie's recommendation, Li invited Sun to work there in 1894. Sun responded with a famous letter to Li on saving the whole nation rather than a handful of patients.<sup>14</sup> Li's apathy convinced Sun's revolutionary determination. After an ill-fated 1895 uprising, Sun went into exile for 16 years. While in London in 1896, he was captured by McCartney and incarcerated in the Chinese Embassy for 12 days, until Cantlie secured his release.<sup>15,16</sup> In 1908, Guangxu (光緒) died mysteriously a day before the death of Cixi. His body contained 2000 times the natural content of arsenic. Meanwhile, from 1907 to 1910, eight consecutive uprisings against the Qing dynasty failed.

The Revolution of 10 October 1911 (辛亥革命) founded a new Republic. Foreign aid was sought, and in 1914 the American Rockefeller Foundation set up the China Medical Board (CMB) to fund public medical schools in the new China.<sup>17</sup> Under the CMB, the PUMC became the best funded among the 21 contemporary medical schools in China. The CMB

was to invest a total of US\$20 million in the PUMC until 1949. Its inaugural seminar (15-22 September 1921) was a national highlight. The proceedings included Faust's and Hata's lectures on the use of arsenic against syphilis, filariasis, leishmaniasis and bilharziasis (Manson's fluke *Schistosoma mansoni*).<sup>18</sup> Sadly, the hospital became the national focus again in 1925, when Sun Yat-sen died in the PUMC of liver cancer. That institution was given the unenviable task of preserving his body for 2 years, without dissection, before a burial could be agreed by all political factions. A combination of arsenic, formalin, and mineral oil may have been the embalming solution. In 1932, the PUMC invited Forkner to work in Beijing.<sup>8</sup> In addition to continuing his work in CML, he also studied leishmaniasis. Fowler's solution was used for both diseases, and listed in the PUMC formulary.<sup>19,20</sup> Forkner returned to the United States in 1938 and served as CMB director from 1943 to 1946. His experience with arsenic treatment of leukaemia was summarised in 1939.<sup>21</sup> Arsenic was effective, but only for chronic leukaemia; and the duration of control was limited by disease transformation and chronic arsenic toxicity.

In March 1912, the Hong Kong College of Medicine became the founding Faculty of the new University of Hong Kong. The high costs of running the PUMC made the CMB rethink on its original plans to set up hospitals in Shanghai and Canton. It decided instead to fund established medical colleges. With the ongoing turmoil in China, the Board surveyed the young faculty in Hong Kong. Between 1922 and 1925, the CMB donated a sum of US\$0.75 million to set up Chairs in Medicine (held by J Anderson) and Surgery (held by K Digby). This literally saved the medical school from bankruptcy.<sup>22</sup> The outbreak of World War II (1937-1945) halted medical teaching in Peking and Hong Kong, and both schools were temporarily relocated to Free China. After the war, in 1948 AJS McFadzean from Glasgow was appointed to the Chair of Medicine in Hong Kong. Meanwhile, in 1950, the PUMC was nationalised by the Communist government and discharged from the CMB. As a result, Stephen KP Chang (張光璧), an infectious disease specialist, a member of Forkner's staff and a PUMC graduate, came from Beijing to teach in Hong Kong.<sup>23</sup> He had worked with EC Faust in the PUMC, and had used Fowler's solution for the treatment of bronchospirochetes.<sup>20</sup>

Given this background, it was not surprising that oral Fowler's solution (known as 'liquor arsenicalis') was prepared in the Queen Mary Hospital pharmacy for the treatment of leukaemia. In fact, such treatment continued until the mid-1950s and was painstakingly documented.<sup>24</sup> In the West, however, two wartime innovations in weaponry, namely radioactive isotopes and nitrogen mustard, had turned into effective anti-leukaemia therapy. Slowly, in Hong Kong and

around the world, the use of arsenic was abandoned and forgotten. However, Fowler's solution was still listed in the 1960 edition of Wintrobe's Hematology and the 1970 British Pharmacopedia.<sup>4</sup> The 1989 11th edition Merck index included Fowler's solution for the treatment of psoriasis and severe asthma.<sup>25</sup>

## Rediscovery of arsenic treatment in China

For China, the Great Leap Forward (1958-60 大躍進) and the Cultural Revolution (1966-76文化大革命) were periods of great turmoil and isolation. This was also true in the medical field, where western anti-leukaemic chemotherapy was largely unavailable. In the autumn of 1971, the Harbin (哈爾濱) government in Heilongjiang (黑龍江) learned that an elderly herbalist in the village of Lindian (林甸 275 kilometres away) was dispensing effective TCM against a wide range of cancers. They sent TD Zhang (張亭棟) to investigate. He endured a 3-day journey by train, truck, and donkey-drawn cart to the village. (Nowadays, Lindian is a spa resort 3 hours by highway from Harbin). The recipe turned out to be a concoction of three elements: arsenic trioxide, mercuric oxide (汞), and toad (蟾) extracts. Notably, mercury and toad toxin are still used today in studies of immunomodulation and the cytotoxic treatment of neoplasms.<sup>26,27</sup> The crude mixture was either topically applied or taken orally. Improvements were observed in liver and colon cancer patients with malignant ascites and bleeding. An intramuscular injection was also available. The latter formulation was produced by a Harbin pharmacist TY Hon (韓太雲) posted to Lindian during the Cultural Revolution. Since it was invented in March 1971, it was named solution No. 713.

News of this novel and cheap panacea generated huge interest. It was tried on a variety of tumours, but rapidly abandoned due its toxicity. Despite the initial set-backs, Zhang, a haematologist, continued his experiments. He tried all permutations of the three ingredients (solutions No. 1 to 7) on various leukaemias. It was quickly shown that arsenic trioxide alone (solution No. 1) was the active component. Like Forkner 42 years ago, initial success was obtained with CML in 1973. The first acute promyelocytic leukaemia (APL) patient was treated in the same year, and remained leukaemia free for the next 20 years. Such remarkable activity in APL was first presented as conference abstracts in Harbin (5 cases) in 1976 (中西醫結合治療急性白血病完全緩解五例臨床紀實) and nationally (22 cases) in 1982 (全國中西醫結合白血病座談會). It was also first documented in provincial and national publications in 1981 and 1984, respectively.<sup>28,29</sup> Such discoveries were reported well before the published work on the treatment of APL with all trans-retinoic acid (ATRA). Pure arsenic trioxide (1% solution) was given intravenously and

registered in China as Ailing No. 1 (癌靈一號).<sup>1</sup> From 1985 to 2005, 1250 APL cases were treated in Harbin University alone.<sup>30</sup> In Beijing, oral As<sub>4</sub>S<sub>4</sub> tablets (Realgar, 白血康) were also introduced from PUMC for APL treatment since 1996.<sup>31</sup> However, the low and variable absorption from their formulation may have resulted in erratic pharmacokinetics. Today both arsenic formulations are licensed in China, for the treatment of haematological malignancies and liver cancer.

Such discoveries were largely unnoticed by the rest of the world, until the reopening of China in the 1980s. In 1988, Shanghai haematologists led by ZY Wang (王振義) gained worldwide acclaim for their pioneering work on ATRA differentiation therapy in APL.<sup>32</sup> The findings actually preceded the complete elucidation of the retinoic acid receptor pathway in APL.<sup>33</sup> Shanghai Ruijin Hospital (上海瑞金醫院) became the epicentre of APL research. The team, led by Z Chen and ZX Shen (陳竺、沈志祥), visited Harbin and went on to meet APL survivors and their physicians (J Ma 馬軍 and TD Zhang). Together, they published a seminal series of papers from 1996, detailing the therapeutic efficacy, pharmacokinetics and mechanism of action of arsenic trioxide for APL.<sup>34-36</sup> Almost overnight, arsenic returned to the world stage.<sup>37</sup>

Within 1 year, the success was repeated in the United States on 12 relapsed APL cases, based on intravenous arsenic trioxide supplied from China.<sup>38</sup> Intravenous arsenic trioxide became the standard treatment for relapsed APL and was produced in-house all around the world. Despite its registration in China, according to published accounts, R Warrell Jr in the US filed a US patent via a company dubbed PolaRx<sup>38</sup> for the 'invention' of arsenic trioxide for APL treatment.<sup>39,40</sup> On 26 September 2000, intravenous arsenic trioxide (Trisenox, Cephalon, PA, US) was approved for treatment of relapsed APL by the US Food and Drug Administration. Months later, PolaRx was sold for US\$15 million to Cell Therapeutics Inc. The brand was later acquired by Cephalon pharmaceuticals in 2005 for the sum of US\$70 million. In 2011, Teva pharmaceuticals acquired Cephalon and its products for US\$6.8 billion. All these led to several consequences. Firstly, the cost of the patent led to inflated prices for Trisenox (US\$410 per 10 mg vial and US\$50 000 for a full course).<sup>39,40</sup> Secondly, local production was halted in most countries, as Trisenox became the only registered product. Thirdly, there were challenges to the patent, since it was launched in the US after all work was undertaken and published in China. Chinese production and supply of intravenous arsenic trioxide continued in Harbin (哈伊達製藥), Beijing (Shanglu 雙鷺製藥) and Taipei (TTY 東洋製藥). Production also continued elsewhere, namely in the Indian city of Ahmedabad (Intas),<sup>41</sup> in Sydney (Phebra), and in Teheran.<sup>42</sup> The retail price

ranged from US\$10 to US\$400 per 10 mg. Regrettably, in less developed countries where these products are unavailable or unaffordable, unnecessary deaths from APL continue.<sup>43</sup>

## Arsenic reappears in Hong Kong

In 1997, Hong Kong was returned to China. At the same time, arsenic returned to Hong Kong. The first patient from Hong Kong to receive arsenic therapy had relapsed APL in 1996. She travelled to Beijing and was treated in the PUMC with ATRA plus Realgar tablets and achieved molecular remission. She returned briefly to Hong Kong and eventually settled in Beijing. Subsequently, in 1998, eight relapsed APL cases in Hong Kong were successfully treated with intravenous arsenic supplied from Harbin via Shanghai.<sup>44</sup> However, the experience with oral *liquor arsenicalis* in Queen Mary Hospital was still remembered by Sir David Todd (達安輝).<sup>24</sup> Arsenic trioxide was still 'in active service' when he left for postgraduate training in Glasgow in 1956, and was replaced by busulphan by his return in 1958. A project to revive the oral formulation was started under YL Kwong (龐沃林) in 1998. Similar to Fockner, he too had lost a medical classmate to leukaemia, this time to relapsed APL. In 1984 that particular house officer died of APL relapse after bone marrow transplantation in London.

The Queen Mary Hospital pharmacy, under R Mak (麥偉明), developed our modern *liquor arsenicalis*. The initial effort to dissolve analytical grade arsenic trioxide into a stable solution proved problematic. Since arsenic trioxide solution had been produced and used before Trisenox in many hospitals around the world, help was sought from K Koo of Vancouver General Hospital. A modified protocol for the standard preparation of arsenic trioxide solution, dating back to 1939, was adopted.<sup>45</sup> Pharmacokinetic studies were performed by CR Kumana (顧崇仁), showing excellent bioavailability. Despite the lower peak levels achieved with oral arsenic, the more prolonged period of absorption resulted in a bioavailability equivalent to the parenteral product.<sup>46</sup> Compared to intravenous arsenic, the lower peak levels resulted in negligible QTc prolongation and superior cardiac safety.<sup>47</sup> This was followed by efficacy trials in relapsed APL patients, where a complete response was achieved in virtually all cases.<sup>48</sup> The inexpensive and convenient revived oral formulation has completely replaced intravenous arsenic in Hong Kong. Subsequently over 150 APL patients (age 6 to 83 years) have been successfully treated, taking their dosages of arsenic at home. A patent for the oral formulation was filed via the Versitech Company (港大科橋) in 2003 and approved by the US patent office on 21 April 2009 (no. 7521071 B2). This was followed by the registration of

oral arsenic trioxide in Hong Kong for the treatment of haematological malignancies on 28 June 2010 (no. 59724). This was the first prescription drug developed locally to be registered in Hong Kong under the trade name Arsenol (Unicorn Pharma, Hong Kong). Its manufacture conformed to Good Manufacturing Practice and was approved by the Department of Health on 23 August 2011. Pending the final approval of the finished product by the Department of Health, Arsenol is expected to be ready for local, national, and overseas use by the end of 2011.

The success of arsenic salvage of APL prompted investigators to move it upfront. Intravenous arsenic was used for induction treatment of APL in Houston (without chemotherapy), and Shanghai (with chemotherapy), with excellent results.<sup>49,50</sup> The US intergroup trial also showed that arsenic consolidation was superior to chemotherapy alone for post-remission therapy.<sup>51</sup> The convenience of oral arsenic therapy allows these options to be used on out-patients and on a prolonged basis. This approach to APL management is already our standard clinical practice in Hong Kong. Oral arsenic maintenance therapy over 2 years (with total arsenic dosages of up to 1980 mg)<sup>52</sup> has eradicated APL-related deaths in all cases who reached remission after 2006 in Hong Kong. Elderly patients (beyond the age of 70 years) with APL can now receive oral arsenic and ATRA upfront as sole induction therapy, without any chemotherapy. The current follow-up of survivors is over 12 years and there have been no severe adverse effects. As a result, since 1998 allogeneic marrow transplantation has not been performed for APL in Hong Kong.<sup>53</sup> In a reverse journey of collaboration with Sinopharm (國藥集團), Arsenol may soon be supplied by Hong Kong to centres in China for APL treatment. These promising results have also been shared with colleagues from Europe, US, Australia, Asia and Africa, in a landmark meeting in 2010. Oral arsenic trioxide is poised to completely replace intravenous arsenic in all therapeutic settings. Moreover, avoiding the financial burden of a commercial patent allows the prospect of humanitarian supply of Arsenol to APL patients in less-developed countries.<sup>54</sup> The timeline for the production and approval of this novel medication in Hong Kong is being eagerly followed by patients and physicians nationally and internationally.

## Conclusions

The journey of arsenic in China is remarkable both in terms of time and distance. Its paradoxical role as poison and medicine captures the imagination. China has mixed fortunes with the element. Environmental arsenic contamination of water supplies results in toxic complications in many mountainous parts, including Guizhou, Shanxi,

Mongolia, and Taiwan (貴州、山西、內蒙、台灣).<sup>55</sup> On the other hand, many leukaemia patients owe their lives to this infamous element. The next chapter in its therapeutic development is keenly awaited. It is our duty in Hong Kong to make this product expediently available for worldwide use. For many APL patients in China and around the world, time is running out.

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### Declaration

No conflicts of interest were declared by the author.

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