Special Report

Top five medical innovations in China mainland since *Xinhai* revolution [1911]: results of AME survey-002

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Objective: This survey aims to scrutinize important medical innovations in Chinese mainland since *Xinhai* (*Hsin-hai*) revolution in 1911, which marked the end of Manchurian imperial rule and the beginning of China's republican era.

Methods: An online cross-sectional survey was carried out during the period of Dec 29, 2014 to Feb 5, 2015, totaling 37 days. The survey was conducted on the platform provided by DXY (www.dxy.cn), which is the largest medical and paramedical related website in China. An email was sent to all DXY registered users to invite them to participate in a 5-minute survey. The participants were asked to nominate up to four important medical innovations in China mainland since *Xinhai* revolution. The participant could select 'zero' which means he/she felt there was no important medical innovations, or he/she did not know important medical innovations. It was noted that important medical innovations refer to (I) those with practical and almost immediate significance to improve healthcare; (II) should not only be introducing western technique to China, but those involve major improvement of existing western techniques count; (III) should not be those with important theoretical discovery but did not have almost immediate significance to improve healthcare.

Results: In total 1,513 DXY users participated in the voting. Totally 489 (32.3%), 441 (29.1%), 342 (22.6%), 150 (9.9%), 91 (6.0%) participants provided 0, 1, 2, 3, 4 nominations respectively. (I) Artemisine (Qinghaosu) for malaria treatment (Project 523 team, 1972); (II) arsenic Trioxide (As_2O_3) for acute promyelocytic leukemia (APL) treatment (ZHANG Ting-Dong and colleagues, 1970s); (III) limb re-plantation (CHEN Zhong-Wei and colleagues, 1963); (IV) all-trans retinoic acid (ATRA) for APL treatment (WANG Zhen-Yi and colleagues, 1988); and (V) Wu's mask for plague prevention (WU Lien-The, 1910), were voted as the top five innovations in China mainland since *Xinhai* revolution, with 375, 96, 91, 53, and 8 votes respectively.

Conclusions: In this voting exercise, five achievements were voted as top innovations in China mainland since *Xinhai* revolution. However, only ATRA for APL treatment was accomplished after the ending of *Great Proletarian Cultural Revolution* in year 1976 in China.

Keywords: Technology innovation; history of science; history of technology; inventions and discoveries; dialectics of nature

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Introduction

The history of medicine in last century ranks as one of the most impressive epochs of human achievement. According to Le Fanu (1), important medical innovations in the past century include, but not limited to the following: 1935: sulphonamides; 1941: penicillin; 'Pap' smear for cervical cancer; 1944: kidney dialysis; 1946: General anesthesia with curare; 1947: the linear accelerator for radiotherapy; 1948: intraocular lens implants for cataracts; 1949: cortisone; 1950: smoking identified as the cause of lung cancer; tuberculosis cured with streptomycin and PAS; 1952: the Copenhagen polio epidemic and the birth of intensive care; chlorpromazine in the treatment of schizophrenia; 1954: the Zeiss operating microscope; 1955: open-heart surgery; polio vaccination; 1956: cardiopulmonary resuscitation; 1957: factor VIII for hemophilia; 1959: the Hopkins endoscope; 1960: oral contraceptive; 1961: levodopa for Parkinson's; Charnley's hip replacement; 1963: kidney transplantation; 1964: prevention of strokes; coronary bypass graft; 1967: first heart transplant; 1969: prenatal diagnosis of Down's syndrome; 1970: neonatal intensive care; cognitive therapy; 1971: cure of Childhood cancer; 1973: computerized tomography scanner; 1978: first test-tube baby; 1979: coronary angioplasty; 1984: helicobacter as the cause of peptic ulcer; 1987: thrombolysis for heart attacks; 1996: triple therapy for AIDS; 1998: viagra for the treatment of impotence. The current authors would like to add: magnetic resonace imaging (1976 Sir Peter Mansfield, 1973 Pauil Lauterbur, and 1977 Raymond Damadian); interventional radiology (1953 Sven Seldinger; and 1963 Charles Dotter). The important achievements in medicine during 1851-1900 as described by Charles Murray are enlisted in the Supplementary 1 (2).

This current survey aims to scrutinize important medical innovations in Chinese mainland since *Xinhai* (*Hsin-hai*) revolution in 1911, which marked the end of Manchurian imperial rule and the beginning of China's republican era.

Materials and methods

An online cross-sectional survey was carried out during the period of Dec 29, 2014 to Feb 5, 2015, totaling 37 days. The survey was conducted on the platform provided by DXY (www.dxy.cn), which is the largest medical and paramedical related website in China. This website officially has slightly more than one million users. However, some users could be 'silent' users who were not active, also the possibly double or even triple registration of one same user could exist, therefore the number of active users remained unknown to the authors. An email was sent to all DXY registered users to invite them to participate in a 5-minute survey. To increase the participation rate, a token bonus would be awarded to the DXY users who completed this survey. This token bonus allows the user to download materials from DXY website.

A questionnaire was designed for this survey. The participants were asked to input the demographic characteristics of participants, including geographical area, hospital class, specialty, and their current professional grade. Then the participants were asked to nominate up to four *important* medical innovations in China mainland since *Xinhai* revolution. The participant could select 'zero' which means he/she felt there was no important medical innovations, or he/she did not know important medical innovations took place in China mainland since *Xinhai* revolution. For those participants who select one or more than one innovations, they were asked to name the innovations, while the name of the inventor and the year of innovation were optional. After reading the e-mail from DXY, it was advised that participants took a few days to consider the answers, and then fill the questionnaire. The initial intention was, based on the number of votes, to select ten important medical innovations by China mainland doctors or scientists since *Xinhai* revolution.

It was defined that important medical innovations refer to (I) those with practical and almost immediate significance to improve healthcare; (II) should not only be introducing western technique to China, but those involve major improvement or revision of existing western techniques count; (III) should not be those with important theoretical discovery but did not have almost immediate significance to improve healthcare; (IV) publications in high impact journals itself is not enough to be counted; (V) normally does not involve mass campaign.

All nominations with more than one vote were considered carefully by the authors, with literature search both in English and in Chinese, as well as consultations with peer colleagues.

Results

In total 1,513 DXY users participated in the voting, which is approximately similar to the survey AME survey-001 (1,513 *vs*. 1,663). Distribution of voters from different regions of China is shown in *Figure 1*. The voters' specialty

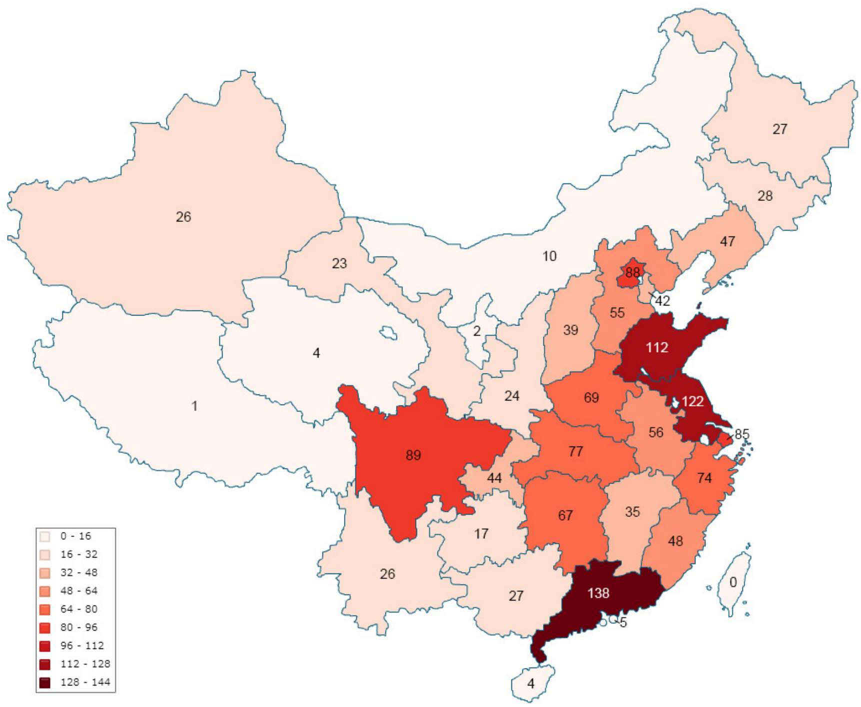

Figure 1 Distributions of voters from different regions of China. Two oversea voters are not included in this map.

distribution included internal medicine (33.5%), surgery (26.2%), oncology (5.1%), anesthesiology (4.56%), radiology (4.5%), emergency medicine (4.2%), obstetrics & gynecology (3.0%), pediatrics (2.6%), research centers (2.4%), laboratory medicine (2.3%), pharmacy (2.0%), ENT surgery (1.7%), dentistry (1.2%), dermatology (1.1%), pathology (0.9%), rehabilitation (0.9%), primary care (0.8%), ophthalmology (0.6%), psychiatry (0.5%), and others (1.6%). The distribution of voters in different class of hospitals was 75.9% from Class III hospital, 16.1% from Class II hospital, 2.6% from Class I hospital, and others 5.4%. The distribution of voters in professional grades class was 4.6% for principle doctors, 13.1% for associate principle doctors, 30.5% for attending specialists, 25.6% for trainee doctors, and 16.2% others. The others included graduate students of clinical specialties as well as medical sciences, nurses, hospital administers, etc.

In this survey, 489 (32.3%), 441 (29.1%), 342 (22.6%), 150 (9.9%), 91 (6.0%) participants provided 0, 1, 2, 3, 4 nominations respectively. Chi-Square test showed that higher rank participants were more likely to give more nominations than junior participants ($P<0.001$, *Figure 2*).

Chemical synthesis of crystal bovine insulin (1965, 473 votes) by the Institute of Biochemistry and the Institute of Organic Chemistry in Shanghai, and Beijing University, as well as the culture of *chlamydia trachomatis* in the yolk sac by Dr TANG Feifan (1957, 39 votes) were considered scientific achievement instead of medical innovation by the authors of this paper. Acupuncture anesthesia obtained seven votes, however, it is not used clinically due to its marginal effect, and therefore it could not be formally counted. According to this survey, (I) artemisine (*Qinghaosu*) for malaria treatment (*Project 523* team, 1972); (II) arsenic Trioxide (As_2O_3) for acute promyelocytic leukemia (APL) treatment (ZHANG Ting-Dong and colleagues, 1970s); (III) Limb re-plantation (CHEN Zhong-Wei and colleagues, 1963); (IV) all-trans retinoic acid (ATRA) for APL treatment (WANG Zhen-yi and colleagues, 1988); and (V) Wu's mask for plague prevention (WU Lien-The, 1910) were voted as the top five innovations in China mainland since *Xinhai* revolution, with 375, 96, 91, 53, and 8 votes respectively (*Figure 3*). The timeline of these achievements excluding acupuncture anesthesia is shown in *Figure 4*.

Discussion

Though initially we hoped to nominate 10 important medical innovations in Chinese mainland since *Xinhai*

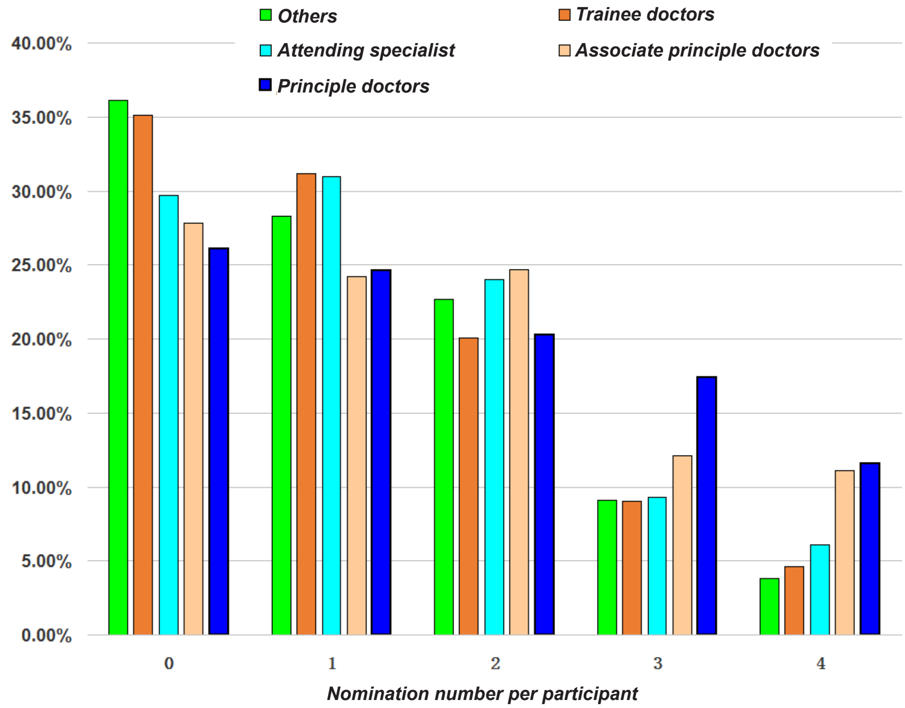

Figure 2 Higher rank participants were more likely to give more nominations than junior participants (Chi-Square test: P<0.001).

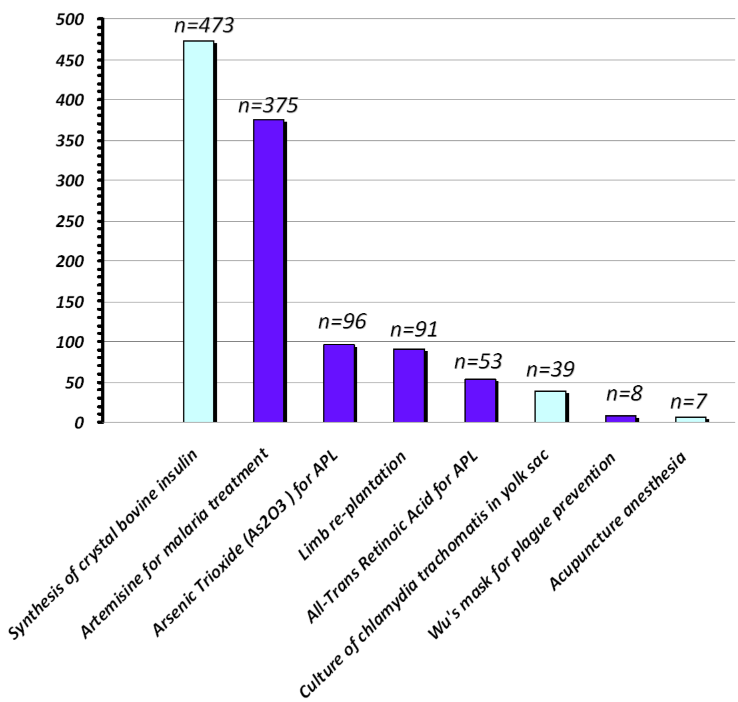

Figure 3 Nominations of important medical innovations in Chinese mainland since *Xinhai* revolution. The total synthesis of bovine insulin in crystalline form and culture of *chlamydia trachomatis* in the yolk sac are considered to be considered scientific achievements instead of medical innovation. Acupuncture anesthesia is not counted due to it is not widely used in clinics. APL, acute promyelocytic leukemia.

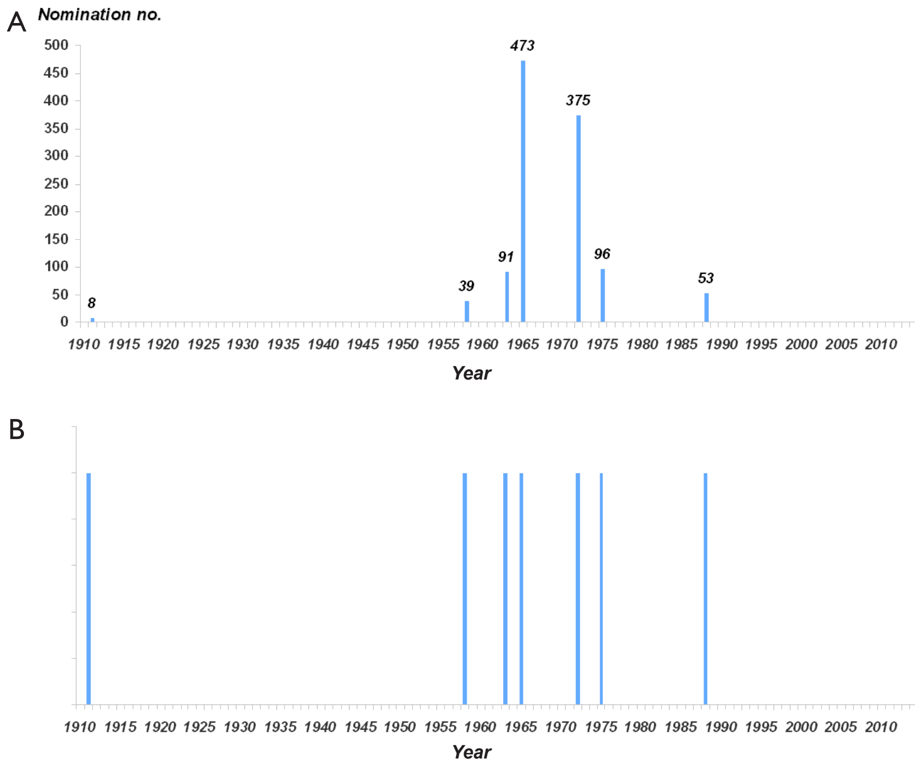

Figure 4 The seven important achievements in Chinese mainland since *Xinhai* revolution across timeline. (A) The number of nominations is used in x-axis in the presentation; (B) the weight of nomination number is removed in the presentation.

revolution, finally we could only nominated five innovations based on the online voting results. Although we have read all the nominations, we were not able to in a position to consider many nominations which obtained one vote but are potentially important. There are two reasons for this: (I) we could not rank the nominations with only one vote; (II) we could not rule out the possibility of self-nomination. Except those listed in *Figure 3*, all others obtained more than one nominations had been carefully considered by the authors, and judged not meeting the criteria we initially set, i.e., (I) first time invented in China Mainland after 1911; (II) practical innovation which had almost immediate effect on improving healthcare; (III) which was later adapted and used widely by other peer practitioners at least in China (therefore *important*). Based on the knowledge of the authors, the nominations in *Figure 3* are explained as below.

Chemical synthesis of bovine insulin in crystalline form

The chemical synthesis of bovine insulin obtained the highest number of vote (473 votes). However, this was a scientific achievement, as it did not directly and immediately improved healthcare in China. The chemical synthesis of bovine insulin started through a collaboration of three institutions: the Institute of Biochemistry and the Institute of Organic Chemistry of Chinese Academy of Sciences in Shanghai, and Beijing University. The total synthesis of bovine insulin in crystalline form was accomplished in 1965 (independently of western countries) (3,4).

Internationally, the work published in 1922 by Banting *et al*. presented purified insulin extract suitable for use on human patients (5). Quickly the pharmaceutical company *Eli Lilly* made a breakthrough in extraction process and was able to produce large quantities of highly refined insulin. Purified animal-sourced insulin was the only type of insulin available to diabetics until genetic advances occurred later. Frederick G. Banting and John James Rickard Macleod were awarded the Nobel Prize in Physiology or Medicine in 1923 for the discovery of insulin. However, in 1916, Nicolae Paulescu, a Romanian professor of physiology at the University of Medicine and Pharmacy in Bucharest, developed an aqueous pancreatic extract which, when injected into a diabetic dog, had a normalizing effect on blood-sugar levels (6). It was considered that Paulescu should be awarded the Nobel Prize as well (7).

The primary structure of insulin was determined by British molecular biologist Frederick Sanger (8-11). He was awarded the 1958 Nobel Prize in Chemistry for this work. Helmut Zahn at RWTH Aachen University, Germany and Panayotis Katsoyannis at the University of Pittsburgh, USA, are often credited as the first to synthesize insulin in 1963 (7,12,13).

The first genetically engineered, synthetic "human" insulin was produced using *E. coli* in 1978 by Arthur Riggs and Keiichi Itakura at the Beckman Research Institute of the City of Hope in collaboration with Herbert Boyer at Genentech (14). The vast majority of insulin currently used worldwide is now biosynthetic recombinant "human" insulin or its analogues (15).

Artemisine

Artemisinin also known as *Qinghaosu*, and its derivatives are a group of drugs that possess rapid action against *Plasmodium falciparum* malaria. The drug is also increasingly being used in *Plasmodium vivax* malaria.

Artemisia annua has been used by Chinese herbalists for more than 2,000 years in the treatment of malaria. The earliest record dates back to 200 BC, in the "*Fifty-two Prescriptions*" unearthed from the *Mawangdui* Han Dynasty tombs. Its antimalarial application was first described in *Zhouhou Beiji Fang*, edited in the middle of the fourth century by *GE Hong*. In 1596, *LI Shizhen* recommended tea made from qinghao specifically to treat malaria symptoms in his "*Compendium of Materia Medica*".

In 1967, a plant screening research program, under the name *Project 523*, was set up to find an adequate treatment for malaria. Its major representative was TU Youyou from the Institute of Chinese Meteria Medica at the China Academy of Traditional Chinese Medicine (now known as China Academy of Chinese Medical Sciences) in Beijing. In the course of this research, *Project 523* team discovered artemisinin in the leaves of Artemisia annua (annual wormwood; 1972) (16-18). It was one of many candidates tested as possible treatments for malaria by Chinese scientists, from a list of nearly 5,000 traditional Chinese medicines. TU also discovered that a low-temperature extraction process could be used to isolate an effective antimalarial substance from the plant, which TU says she was influenced by a traditional Chinese herbal medicine source. In 2011 Tu Youyou was awarded the Lasker-DeBakey Clinical Medical Research Award for her role in the discovery and development of artemisinin.

Artemisinin's action mechanism is still under investigation.

In 2013 the pharmaceutical company *Sanofi* announced the launch of a production facility to manufacture the drug on a large scale based on a modified biosynthetic process for artemisinic acid, initially designed by Keasling at the University of California Berkeley and optimized by Amyris (a biotechnology firm in California) (19).

Artemisinin has saved countless number of lives, especially in the developing world. The *Project 523* team such made a major contribution to the world (20).

Arsenic trioxide for the treatment of APL

Because of its significant medicinal properties, arsenic has been used as a therapeutic agent for more than 2,400 years (21). Arsenic trioxide (As_2O_3, ATO) has long been of interest, dating to traditional Chinese medicine, where it is known as *Pi Shuang*, and to homeopathy, where it is called arsenicum album (22,23). In the 15th century, William Withering, who discovered digitalis, was a strong proponent of arsenic-based therapies (24).

In the 18th century, Thomas Fowler compounded a potassium bicarbonate-based solution of arsenic trioxide (25). Arsenic's antileukemic activity was first reported in the late 1800s. In 1878 a report from Boston City Hospital described the effect of Fowler's solution on the reduction of white blood cell counts in two normal people and one patient with "leucocythemia" (25,26). Subsequently ATO was administered as a primary antileukemic agent until it was replaced by radiation therapy. However, the hematologic use of arsenic had resurgence in popularity in the 1930s when its efficacy was reported in patients with chronic leukemia (27). Until supplanted by modern chemotherapy, arsenic trioxide after radiation was considered the most effective treatment for leukemia.

In the 1970s ZHANG Ting-Dong and colleagues at Harbin Medical University investigated the potential use of the traditionally used Chinese medicine arsenic trioxide to treat APL (28-31). By 1979, Zhang and his collaborators had reached our current understanding that ATO could treat leukemia, especially APL.

In 1998 Soignet *et al*. (32) treated 12 recurrent APL cases with ATO and observed complete response in 11 cases. The mechanisms were thought to be partial cellular differentiation and apoptosis. The Soignet *et al*. paper helped international acceptance of ATO as a treatment of

APL. Rao *et al.*'s and Au's review papers detailed this story (33,34).

Arsenic trioxide under the tradename Trisenox is now a chemotherapeutic agent approved by the US FDA for the treatment of APL that is unresponsive to "first line" agents, namely ATRA.

In 2003 University of Hong Kong developed a liquid form of arsenic trioxide that can be administered orally (35-38). The convenience of oral arsenic therapy allows these options to be used on out-patients and on a prolonged basis.

Limb replantation

Limb replantation has a long history. In 1814 William Balfour published the first medical report of a digital reattachment. Balfour successfully repaired his son's index, middle, and long fingers, which were partially amputated at the mid-distal phalanx (39). Thomas Hunter is credited with the first thumb replantation performed in the following year. These replantations were performed without vascular anastomosis; thus these fingers likely survived as composite grafts. The theory of spontaneous recanalization occurring in composite grafts was published in 1964 by Douglas and Foster (40).

Experimental work in replantation and vascular anastomosis techniques simultaneously by Halsted, Hopfner, and Carrel in the 1880s supplied the basic principles of vascular surgery (41). Dr. Carrel won the Nobel Prize in 1912 for his work on vascular anastomoses and for pioneering renal transplantation. With further technical advancements in suture material and surgical instruments, primarily the operating room microscope, replantation became more achievable. Harry Buncke is credited with developing the first set of microsurgical instruments, microsutures, and microsurgical needles (42). Jacobson and Suarez in 1960 developed microsurgical vascular anastomosis (43,44).

The first replantation to be performed in the world involved repair of the brachial artery and was done by a team of chief residents led by Dr. Ronald Malt at Massachusetts General Hospital in Boston, USA in 1962. The arm of a 12-year-old child severed at the level of the proximal humerus was reattached (45).

In China the first report of a replantation was reported by a team led by CHEN Zhong-Wei of the Sixth People's Hospital in Shanghai in 1963 (46,47). A machinist's hand was reattached at the level of the distal forearm. In this case vascular couplers were used for the vessels as Dr. Chen and his colleagues did not have good microsutures available at that time. Dr. Chen further developed many other microsurgical procedures, including techniques for reattaching amputated fingers and thumbs, preserving severed extremities, reconstructing muscles and repairing nerves and blood vessels (48-53).

Kleinert *et al*. performed the first digital arteries anastomosis in the revascularization of a partially amputated thumb in 1963 (54). In 1965 Shigeo Komatsu and Susumu Tamai were the first to perform such a digit replantation via microvascular reanastomosis procedure (55).

ATRA for the treatment of APL

The story of ATRA for APL has been well documented (33,56). In 1980 Breitman *et al*. (57) discovered that ATRA and 13-cis retinoic acid induced HL-60 differentiation into mature cells, while Vitamin A was 1,000-fold less effective. In 1981 Breitman *et al*. (58) tested drug sensitivity of leukocytes from the peripheral blood of two patients with APL and found that cells induced to differentiate by ATRA. In 1983 Honma *et al*. (59) reported ATRA was among those capable of inducing the differentiation of leukocytes from APL patients. Koeffler (60) in 1983 summarized *in vitro* studies including cellular differentiation by retinoic acid and other chemicals, viewing ATRA and 13-cis retinoic acid as equivalent in differentiating APL leukocytes. Single cases of APL treatment by 13-cis retinoic acid were reported in 1983, 1984, 1986, respectively (61-64).

In 1987 WANG Zhen-Yi of Shanghai Second Medical College used ATRA reported the use of ATRA (alone or in combination) for the treatment of six APL patients (65). In 1988 Wang's group published their use of ATRA in the treatment of 24 APL patients in *Blood* (66).

In 1989 Chomienne *et al*. (67) compared the effects of ATRA and 13-cis retinoic acid with two APL patients for each chemical and felt that ATRA were more effective. In 1990 the same French group reported that ATRA was more effective than 13-cis retinoic acid (68). The effect of ATRA was also confirmed by Chinese doctors (69). In 1991 Warrell *et al*. (70) replicated the findings of the Wang group in China and the Degos group in France. In 1997 Tallman *et al*. (71) reported their studies of 346 APL patients, in which they compared the therapeutic effects of ATRA and the previously standard chemotherapy with daunorubicin and cytarabine, and found it to be more effective if ATRA was used for both induction and maintenance.

ATRA with chemotherapy is now the standard of care for APL. Recently, a phase 3, multicenter trial comparing ATRA plus chemotherapy versus ATRA plus arsenic trioxide showed ATRA plus arsenic trioxide was superior to ATRA plus chemotherapy in the treatment of patients with low-to-intermediate-risk APL (72). A randomized clinical trial compared efficacy and toxicity of ATRA plus chemotherapy versus ATRA plus arsenic trioxide in APL patients, and quality-of-life results supported the use of ATRA plus arsenic trioxide as preferred first-line treatment in patients with low- or intermediate-risk APL (73).

Culture of chlamydia trachomatis in the yolk sac

In 1904 a mild, non-gonococcal urethritis was described by Waelsch in Prague, and few years later urethroscopic nodules similar to those in trachoma were found (74,75). In 1907 Ludwig Halberstaedter and Stanislaus von Prowazek described intracytoplasmic inclusions in conjuctival scrapings from orangutans following infection with a male patient's ocular scraping who suffered from trachoma (76). When it was found the newly discovered intracellular agent was filterable and was cultivable only in animals they regarded this pathogen as a virus. This theory was widely accepted until the mid 1960s. In 1909, Halberstaedter and von Prowazek described first an agent similar to that of trachoma virus, detected in a case of neonatal blenorrhoea (77). In the next year, Frietsch *et al*. and Heyman published cases of neonatal conjunctivitis with trachoma-like inclusions in conjunctival scrapings of neonates, and cervical scrapings of their mothers (78,79).

The first definition given to the causative agent of trachoma by Halbersaedter and von Prowazek in 1907 has been changed several times. In 1935 Busacca cited them as Rickettsia trachomae expressing the morphological similarities between the trachoma agent and rickettsiae (80). In 1945 Jones *et al*. introduced the term *Chlamydia* (81). The first contemporary species name, *C. trachomatis* and the family name, *Chlamydiaceae* were proposed by Rake in 1957. Page and Storz introduced the higher taxonomic rank *Chlamydiales* and classified the causative agent of psittacosis into the *Chlamydia psittaci* species (82,83). In the mid 1960s it was proven that these agents are actually bacteria (84).

The differential stain for the detection of rickettsiae and chlamydial elementary bodies in tissue samples was proposed by Castaneda in 1930 (85). This method resulted in the morphologic separation of these small intracellular bacteria from the viral inclusions. Until the early 1970s, these stains were the only direct detection diagnostic methods for the chlamydial infections.

Between 1931 and 1935, Woodruff and Goodpasture applied embryonated hen's eggs for successful cultivation of poxviruses (86). This culture method was further developed and applied for different viruses by Burnet *et al*. in the 1930s (87). Burnet and Rountree cultivated successfully the causative agent of psittacosis in the chorio-allantoic membrane of developing chick embryo the first time in 1935 (87). In the same year, Miyagawa *et al*. cultivated first the causative agent of lymphogranuloma inguinale using the same method of egg inoculation (88). Rake *et al*. managed to reproduce this experiment in the yolk sac of the developing chick embryo in 1940 (89).

For long time, the attempts to cultivate trachoma virus in embryonated eggs failed. In 1957 Dr. TANG Feifan *et al*. at National Vaccine and Serum Institute in Beijing succeeded to cultivate trachoma virus in the yolk sac (90,91). This experiment was reproduced by Collier and Sowa in 1958 (92). Finally in 1959 the agent of inclusion conjuctivitis was successfully isolated by Jones *et al*. (93).

The agent of lymphogranuloma venerum was shown to be susceptible to the sulphonamides by MacCallum and Findlay in 1938 (94). Thygeson reported successful treatment of adult and neonatal inclusion conjunctivis with sulfanilamide (95). Researchers later found superiority of the tetracyclines against chlamydiae over other antibiotics (96). At present, an oxytetracycline derivative, doxycycline is one of the most effective broad spectrum antibiotic against intracellular bacteria including chlamydiae beside macrolides, fluoroquinolones and rifampicin (74).

Wu's mask and plague prevention

Dr. WU Lien-The was born in Penang, on 10 March 1879, in Malaysia. He was the first Chinese medical student at the University of Cambridge. Dr. Wu graduated in 1902 then pursued his interest in Bacteriology in Germany and France. Upon returning to Malaysia after a year in the Institute of Medical Research in Kuala Lumpur, Dr. Wu worked as a doctor in Penang, where he put money and effort into rehabilitation of opium addicts. In 1908, he accepted the offer to be Vice-Director of the Imperial Army Medical College in Tianjin, China. In 1910, he was sent to Manchuria, in harsh winter, to fight the terrifying pneumonic plague. Within 4 months and a death toll limited to 60,000, he brought the dreaded disease under control with diligent scientific documentation.

Most notably were his invention of the "Wu mask", the cremation of dead bodies and quarantine measures, which lead to plague eradication. On 3 April 1911, he convened and chaired the first international scientific plague meeting at Shenyang. He began to modernize China's medical services and education, founding the Harbin and Beijing Medical Universities and building some 20 modern public hospitals, laboratories and research institutions. He initiated the formation of the Chinese Medical Association, and established the first national quarantine service (97-99).

After Dr Wu's distinguished career in China, he retired back to Malaysia. This probably made his achievements less well known in China mainland.

Acupuncture anesthesia

Now it is established that surgery cannot rely on acupuncture anesthesia solely (100-104). Madsen *et al*. (105) looked at thirteen trials with 3,025 patients in which acupuncture was used to treat a variety of painful conditions. There was a small difference between 'real' and sham acupuncture, and a somewhat bigger difference between the acupuncture group and the no-acupuncture group. However, this bigger difference corresponded to only a 10 point improvement on a 100 point pain scale. A change of this sort is described as a minimal change (106).

Vickers *et al*. (107) did a meta-analysis for 29 RCTs with 17,922 patients. The results were similar to those of Madsen *et al*. (105). Real acupuncture was better than sham, but by a small amount (108).

One observation from the current study is that out of the 8 nominations discussed in this paper (including 3 scientific achievements), only ATRA for APL treatment by WANG Zhen-Yi *et al*. was accomplished after the ending of Great Proletarian Cultural Revolution, which ended 38 years ago in 1976.

One potential methodology conflict is that we asked the participants to nominate important innovations; however, being *important* or not is a subject judgement. There are some *important* innovations might be missed in this survey, particularly that we could not scrutinize those with only one nomination. Some important innovations may remain to be further recognised by the medical professionals in China. Other limitations include that the number of participants is still small; and principle doctors and associate principle doctors count only for 4.6% and 13.1% of the total voters.

While important contributions have made, such as artemisinin for malaria treatment and arsenic trioxide for APL treatment, considering the population size and economic size of China the overall achievements did not shine compared to Euro-American countries. If we look at the past history, in the article entitle '*The Statistical Characters of Science and Technology in the History of China*' Dong *et al*. (109) concluded that (I) the accumulated technological inventions of China account for 5.8% of the world total, which are much less than those of North America and Europe, and also less than those of the Middle East; (II) the accumulation of scientific achievements over Chinese history is less than 1% of the world total; (III) technological activities in China have been active from the Warring States Period (800 BC) to the end of the Song dynasty (1,300 AD). After that, the technological innovations have fallen into stagnation; (IV) the European area has been active in various scientific activities since 500 BC, and its scientific and technological achievements have always been outperforming China. Similar accounts have been well illustrated by Charles Murray in his book 'Human Accomplishment: The Pursuit of Excellence in the Arts and Sciences, 800 BC to 1950' (2). Murray noted that '*what the human species is today it owes in astonishing degree to what was accomplished in just half a dozen centuries by the peoples of one small portion of the northwestern Eurasian land mass*' [(2) page 264].

A London School of Economics and Political Sciences scholar published in 2006: "*Some argue that the ideographic Asian languages curb abstract thinking and creativity among Asians. Others point out that Asian cultures, religions, and educational systems devalue and discourage logical thinking. Science is… inherently elitist. A nation does not dominate science by having a large number of people… and there appears to be a dearth of good, original, scientific ideas in Asia in the last century*". As we previously mentioned, while Japan and South Korea have first-class carmakers and electronics companies, Japanese and South Korean pharmaceutical companies are much less visible (110). For the year of 2013 of the 10 top pharmaceutical companies none of them were Japanese or Korean; and of the 25 top biotech companies none of them were Japanese or Korean (111,112), despite the fact that Japan has been a major geopolitical and economic power since early 20th century and till now produced seven noble prize winners in chemistry and ten Noble prize winners in physics. Also while China currently produced much more citable publications, innovative pharmaceuticals and biologics are stronger in India than in China (113).

It is important to recognize China's relative strength and relative weakness as much as possible. This will help to correctly position China, and thereafter move forward wisely, and probably overcome China's relative weakness. Murray noted that '*history has worked out, the ages rich in giants have also been rich in near-giants and the rest of the significant figures*…. ' [(2) page 249], i.e., the periods which have a lot of great innovators have also a lot of excellent innovators and good innovators as well. This is, in small part, reflected in *Figure 4*. While certainly allowing exceptions, at the time of writing this paper the authors have to be pessimistic, and feel it is unlikely that in the coming future China will contribute a large portion of Nobel Prize winners in physiology and medicine with a series of major original contributions to medicine. If it happens, following the same model of Japan, China will more likely have Nobel Prize winners in physics and chemistry initially. Following the same models of Japan and South Korea, Chinese companies will likely do better in mechanics and electronics instead of pharmaceuticals and biologics. However, this issue is rather complicated and convoluted; the current authors certainly avoid drawing any firm conclusion. The future projection will remain unknown until it has been realized.

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Disclosure:
(I) The primary aim of this study was not to accurately document the history of medicine in modern China; instead, it was to document the voting exercise. The authors did not exhaustively search the original documents for the items discussed in this paper. The authors acknowledgement that the literature references in the paper may not be well-balanced; (II) Besides original innovations, the authors acknowledge that timely introducing Western technologies to China is also equally important and cost-effective; (III) Chemical synthesis of crystal bovine insulin [1965] as well as the culture of *chlamydia trachomatis* by Dr. TANG Feifan [1957] were considered scientific achievements instead of medical innovation by the authors of this paper. Due to the limitation of the authors' knowledge on synthetic chemistry and microbiology, the authors could not fully annotate the full importance of these two scientific achievements. In addition, the authors highly respect Dr. TANG Feifan for his other contributions to the medical care in China.

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Supplementary 1

Central Events in Medicine during 1851-1900 (Murray C, *Human Accomplishment: The Pursuit of Excellence in the Arts and Sciences*, 800 B.C. to 1950'. Page 212-213):

(I) 1851: Germany, Hermann Helmholtz invents the ophthalmoscope.

(II) 1853: Scotland, Alexander Wood and Charles Pravaz invent the hypodermic France syringe.

(III) 1854: England, Florence Nightingale founds modern nursing practice.

(IV) 1856: France, Louis Pasteur invents pasteurization.

(V) 1862: France, Louis Pasteur, the germ disease theory, transforming the course of medical research and practice.

(VI) 1863: France, Casimir Davaine discovers the microorganism that causes anthrax, the first linkage of a disease with a specific microorganism.

(VII) 1863: Germany, Johann Baeyer discovers barbituric acid, the first barbiturate

(VIII) 1865: England, Joseph Lister introduces phenol as a surgery disinfectant, reducing the death rate from 45% to 15%.

(IX) 1865: France, Claude Bernard's Introduction à l'Etude de la Médecine Expérimental is instrumental in establishing medicine as a science with observation, hypothesis, and experimentation.

(X) 1874: USA, Andrew Still discovers that dislocations of the vertebrae are a source of disease, founding osteopathy.

(XI) 1876: Germany, Robert Koch demonstrates that bacilli are the cause of anthrax.

(XII) 1881: France, Louis Pasteur invents anthrax inoculation, the first effective treatment of an infectious disease with an antibacterial vaccine.

(XIII) 1881: Austria, Christian Billroth successfully excises a cancerous pylorus, beginning intestinal surgery; sometimes said to be the beginning of the modern era of surgery.

(XIV) 1881: Germany, Robert Koch introduces steam sterilization.

(XV) 1881: USA, William Halsted conducts the first known human blood transfusion.

(XVI) 1882: Germany, Robert Koch isolates the tubercle bacillus.

(XVII) 1884: Austria, Sigmund Freud and Carl Koller use cocaine as a local anesthetic.

(XVIII) 1884: England, Rickman Godlee surgically removes a brain tumor.

(XIX) 1884: Germany, Edwin Klebs and Friedrich Löffler isolate the bacterium for diphtheria and identify it as the causative agent.

(XX) 1885: France, Louis Pasteur invents a rabies vaccine.

(XXI) 1887: France, Augustus Waller records the electrical activity of the heart, founding electrocardiology.

(XXII) 1890: Germany, Emil von Behring develops the first antitoxin, for tetanus.

(XXIII) 1891: Germany, Japan, France, Emil von Behring, Kitasato Shibasaburo, and Émile Roux develop an antitoxin for diphtheria.

(XXIV) 1893: USA, Daniel Williams conducts the first successful heart surgery on a human.

(XXV) 1896: Germany, Hermann Strauss introduces X-rays for diagnostic purposes.

(XXVI) 1896: Germany, Ludwig Rehn successfully sutures a wound in a human heart.

(XXVII) 1896: Italy, Scipione Riva-Rocci invents the mercury sphygmomanometer, the precursor of modern version.

(XXVIII) 1896: Netherlands, Christiaan Eijkman discovers that beriberi is caused by a dietary deficiency.

(XXIX) 1897: England, Ronald Ross discovers the malaria parasite in the anopheles mosquito.

(XXX) 1899: Sweden, Tage Sjogren achieves the first proven cure of a patient by X-ray treatment.

Supplementary 2

Annotation of English translation of Chinese names in the text

Xinhai (Hsin-hai) revolution: 辛亥革命

Fifty-two Prescriptions: 五十二病方

Mawangdui: 马王堆

Zhouhou Beiji Fang: 肘后备急方

GE Hong: 葛洪

LI Shizhen: 李时珍

Compendium of Materia Medica: 本草纲目

TU Youyou: 屠呦呦

Pi Shuang: 砒霜

ZHANG Ting-Dong: 张庭栋

CHEN Zhong-Wei: 陈中伟

WANG Zhen-Yi: 王振义

TANG Feifan: 汤飞凡

WU Lien-The: 伍连德

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