War In Developing Drugs: A Case Study In Connection

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Abstract

Truly someone said that “Necessity is the mother of invention”. Scientific evolution always comes with sociological need and temporary crisis in our daily life. The invention of fire, wheel for transportation, paper for documentation, each and every scientific invention is associated with some sociological need. Even these words are very true for discovery of medicines. It was until the starting of twentieth century i.e. the world war, which caused proper things and brought sufficient human attention towards the need of developing new medicines (Drugs) and medicinal techniques. In this article we shall try to reveal the very history with a strong emphasis on the chronological sequence.

Keywords: Tropical disease, War, Pharmaceutical revolution, Malaria, Tuberculosis, Fungal infection, Viral infection, Cancer, Anesthetic and analgesic agent, Vaccine.

Introduction

The Old Days:

From the very beginning of human evolution the philosophy regarding ‘Disease, Medicine and Cure’ was same. Something which could cure an ailment was considered to be a medicine. But the problem was those so called medicines were not well characterized, their side effects were not well studied; even the dosage were not standardized. In the cases of a few diseases the treatments were not known because of not having proper investigation on the field. In those days, medicines were generally plant-extracts which were not well characterized. Discovery of these so-called-medicines majorly involved trial and error method without proper background of investigation. With time new diseases like Cancer, Tuberculosis and others also came to the picture but we were helpless because we didn’t have proper idea how to treat a disease, how to look for a medicine without going for less efficient ‘trial and error method’.

The World in Wars:

War has been an unseparated part of our life across the century. In earlier days we fought for food, cloth and shelter, later Nations fought for power, which lead to major destruction. Millions of people died, billions were about to die and these things made people realize the necessity of developing new drugs and surgical methods. Between 1800 and 1950 there were around 450 wars recorded in history and among those a few of those are really important from the view point of developing medicinal science and history [1]. Few of those are_

- Canadian War of 1812 (1812-1815)
- Crimean War (1853-1856)
- American Civil War (1861-1865)
- Second Boer War (1899-1902)
- World War-I (1914-1919)
- World War-II (1939-1945)
- Korean War (1950-1953)

> "more than one great war has been won or lost not by military genius or ineptitude, but simply because the pestilence of war - from smallpox and typhoid to cholera, syphilis, diphtheria, and other scourges - reached the losers before they infected the winners".
> **Source:** A. Chase. Magic Shots, William Morrow and Company, New York, 1982: 197.

Millions of people died throughout the whole of 19th and 20th century not only by bullets or grenades but also of tropical diseases. In a few cases effect of unexpected outbreak of diseases in the battlefield were so prominent that they even changed the political scenario of the world. From the examples given in table-1 it is very clear that major attention was needed for developing medicines to tackle the situation.

Table-I: Casualties due to diseases in war. [2-7]

War	Total Death	Death due to disease	% of death because of disease
[a]American Revolutionary War	25000	17000	68
[b]Canadian war of 1812	5100	3500	69
[b]Crimean war	22000	16000	73
American Civil War	620000	410000	66
[a]Second Boer War	18000	11500	64
[a]World War I	116500	63000	54

[a]Fatality of American soldiers only

[b]Fatality of British soldiers only

Realizing the intensity of the situation, governments took many steps like new committees were built, funds were provided, pharmaceutical and medical experts were recruited. Specially during world war many organizations were established as a step towards developing medicinal science. In US many organizations came to picture. Among those National Research Council (1916), Committee on Medical Research (1941), Office of Scientific Research and Development (1941) and War Research Service (1942) played the most important role [8-11]. Funding for army medical research was increased in an unexpected rate. For example, in US it was raised from $16000 (in 1940) to $37000 (in 1942) within 2 years [12]. In some cases individuals built industries with their hard effort and earned millions-billions by supplying their products in battle fields.

Parallel to the advancement of medicinal science, progress was also made in the field of treatment and management of battlefield casualties. For example, during Canadian War, in 1814 a formal medical department was established by the US army to tackle deaths caused by infection and major wounds in battlefield [13]. Four decades later in 1859 ambulance was introduced and after that numerous other innovations came throughout the whole 20th century which impressively pulled down battlefield fatality [14]. One statistics says that from World War I(1914-1919) to Gulf War(1991) i.e. just within 70 years ratio of deaths caused by infectious diseases to battle field and wound deaths decreases by a factor of 40 [15].

In this way war became very constructive in developing medicinal science and very soon we will find that these consequences probably were the best which could have happened to the society at that time.

Rise of Pharmaceutical Industry:

From the 30s of the 19th century some pharmaceutical companies were built based on simple techniques like extraction, purification of natural products from natural resources. Along with preparing a few medicines like stuffs, like ointment, bark powder etc. they isolated some compounds like Morphine, Colchine form plants. Most of them were built in individual interest with minimum number of workers. But in the 1860s pharmaceutical companies involving thousands of employees came to the picture, even a few of those are still one of the best pharmaceutical companies of the world.

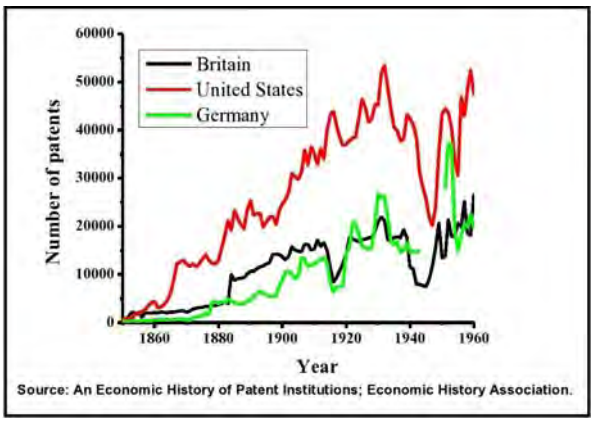

Fig. 1: Number of patents received during 1850 to 1960

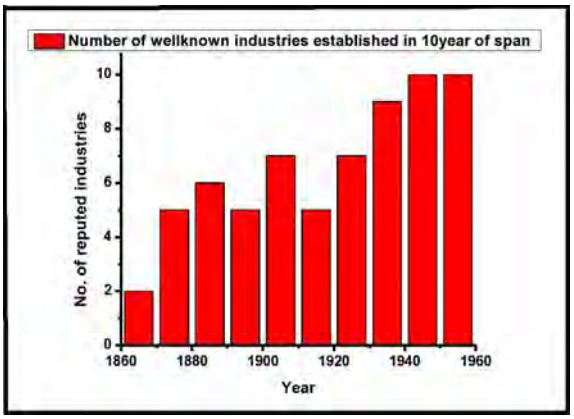

Fig. 2: Number of wellknown pharmaceutical industries established in 10 year of span.

The first period of pharmaceutical revolution came in Germany, Switzerland, Italy, United States, Belgium and Netherlands [16]. Within 1860 to 1960, thousands of companies were established and among those a few are still act as a power house of pharmaceutical industry. Johnson and Johnson (1885), Abbott Laboratories (1888), Eli Lilly (1876), Bayer pharmaceuticals (1863), Bristol-Mayers (1887), Hoffmann-La-Roche (1896), Pfizer (1950) stands among top 15 pharmaceutical industries according to their 2013 annual report [17]. Name of a few popular industries grown up at that period are listed below in Table-II.

Table II: List of Pharmaceutical industries with their year of establishment.

Name	Year	Name	Year
Wyeth	1860	Bial	1924
Bayer	1863	Yuhan Co. Ltd.	1926
Nycomed	1874	Weleda	1928
Shionogi	1874	UCB	1928
Mycomed	1874	Baxter International Inc	1931
Eli Lilly and Company	1876	Goody	1932
Burroughs Wellcome & Company	1880	Interpharma	1933
Boehringer Ingelheim	1885	Cipla	1935
Johnson and Johnson	1885	Cilag	1936
Danippon Pharmaceuticals	1885	Eisai Co.	1936
Bristol-Myers	1887	Alkaloid	1936
Perrigo Company	1887	Grifols	1940
Abbott Labratories	1888	Takeda Kasei	1940
Merck	1891	Almirall	1943
Purdue pharma	1892	Alcon	1945
STADA Azneimittel	1895	United Laboratories	1945
Hoffmann-La-Roche	1896	Allergan	1948
Fenjal	1899	Kyowa Hakko Kirin	1949
Gedeon Richter	1901	Ipca Laboratories	1949
Teva Pharmaceuticals Indus	1901	Medtronic	1949
3M	1902	Ferring Pharmaceuticals	1950
Glaxo	1904	Jenapharm	1950
Black Drug	1907	Pfizer	1950
L'Oreal	1909	Bosnalijek	1951
Zandu Realty Limited	1910	Cadila Healthcare	1952
Fresenius SE and Co.	1912	Takeda	1952
Sigma Pharmaceuticals	1912	Janssen	1953
Lundbeck	1915	Ego Pharmaceuticals	1953
CSL Limited	1916	Straumann	1954
Orion Corporation	1917	Sequare Pharmaceuticals	1958
Pliva	1921	Torrent Pharmaceuticals	1959
Novo Nordisk	1923	Valent Pharmaceuticals	1960
Astellas Pharma	1923	Tyco Healthcare	1960

The Milestones:

Development of anti-malarial drugs

Malaria was a very common disease and during the 19th century it was a major threat. As a treatment, Cinchona bark was well known and it was the only so called medicine available at that time. Before that cinchona bark was used as a fever relief agent. People from Peru first applied it on malaria affected patients and accidentally it was found to be effective [18]. But the problem was distinguishing cinchona from other trees, which was really tough to common people. Even barks from other trees which were bitter in taste (as cinchona is) were also given to the patients just following the trial and error method, but those were found to be ineffective. Other than these, different trees under the cinchona species were also found to have different anti-malarial activity. These observations lead to the discovery of the Quinine, which was responsible for anti-malarial activity of cinchona bark. Very soon Charles Ledger found the species *Cinchona ledgeriana*, which had maximum Quinine content [19].

Fig. 3a: Bottle of quinine used in Second World War

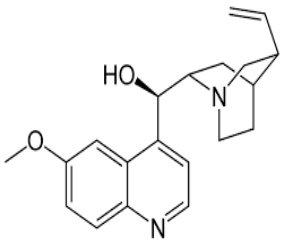

Fig. 3b: Structure of Quinine

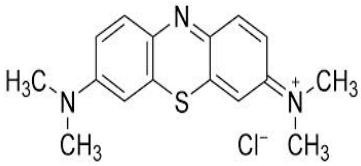

Fig. 3c: Structure of Methylene blue

During 1817-1836 British soldiers had to stay at Sierra Leone and almost half of the troop died there, mostly of malaria. In 1865 Ledger tried to sell seeds of good quality cinchona tree to the British government but they denied. When he approached the Dutch government, they made no mistake. Dutch government was very conscious about what happened to the British army at Sierra Leone. They paid Ledger well for that and took the precaution against malaria for their own army [20]. Very soon Holland became the maximum quinine producing country in the world. Within 1930, the Dutch government reached the milestone of producing around 97% of the world's total Quinine production followed by India (2.5%), whereas rest of the world produced only 0.5% of that [21].

US government used to manage their quinine requirements collecting that from Netherlands. During World War II the Germans took over Netherlands and the Japanese took over Java. As a result Quinine production and supply was greatly affected and US Military troop faced big trouble while working in malaria prone zones. So scientists from America, England and Australia made an attempt to synthesize anti-malarial drugs not being dependent upon its natural resources. Within 1948 they synthesized 3-Methylquinine (Sontochin), Chloroquinine (Resochine), 2-Hydroxynaphthoquinone etc. Very soon after the war Primaquine, Proguanil, Atovaquone etc. came out in market as antimalarial drug. Even a few synthetic moiety discovered during that period served as a prototype for modern anti-malarial drugs, like a compound coded by "SN-10275" (6,8-dichloro-2-phenyl-alpha-2-piperydil-4-quinolinemethanol) was modified to get "Mefloquine" and it was introduced in around 1975 [22]. Proguanil served as a prototype for 'Pyrimethamine' [23]. In 1970 Pyrimethamine in combination with Suladoxime was introduced as 'Fansidar' [24].

Parallel to this classical route of drug discovery one interesting thing happened. In 1880s and 1890s Alphonse Laveran, Ronald Ross, Battista Grassi and others identified the malaria parasite and explained the transmission of malaria to mosquitoes [25]. In 1891 German scientist Paul Ehrlich discovered the anti-malarial activity of the synthetic dye "Methylene Blue" and eventually it was used as an antimalarial drug [26]. But for having a few prominent side effects like turning the urine blue or green or coloration of sclera it was no longer used by practitioners. Methylene Blue was pretty cheap and as a result extensive research started to reveal core functionality for its activity. Very soon Bayer, a dye manufacturing company, became a pharmaceutical company there. They developed Plasmoquine (1925), Mepacrine (1932), Resochin (1934) and Sontochin (1936) etc. using Methylene Blue as a prototype and they became the first generation synthetic drugs in history to be used as an antimalarial agent [27].

Malaria was the first disease to report a "Drug resistance" in history. In World War II Japanese troops used "Atebrine" as an antimalarial drug but in an inadequate dose. As a result mosquitoes got Atebrine resistance and it was no longer effective as antimalarial agent. This very observation opened up a new branch of science. The same happened during Vietnam War when American troops fell in trouble due to drug resistant malaria. After that extensive research was started in the field of drug resistance and alternative discovery at the 'Walter Reed Army Institute of Research, Washington', which later made a landmark in history [28].

Development of anti tuberculosis drug

Tuberculosis is a fatal disease caused usually by a mycobacterium called *Mycobacterium_tuberculosis*. It was first prominently observed during the American Civil War. At that time among the 600,000 soldiers about 6500 died of this disease, but compared to other diseases like Malaria, Typhoid etc. mortality was much less in it. So at that time it was neglected and no progress was made against it.

It took around 60 years to develop the science of tackling tuberculosis, the very consequences of the World War I made the first landmark towards developing the science. In World War I tuberculosis became a severe problem to military persons. Before world war was over, around 2000 soldiers died because of the disease. Government

of France removed their 80,000 soldiers suspecting them to be TB affected. In 1916 Germany reported over 75,000 soldiers diagnosed. Even 50,000 French prisoners became TB patients during World War I [29].

At the end of the World War I, individually nations realized the necessity of developing antiTB treatment. In 1918 National Tuberculosis Association was established as the first step [30]. Within 25years after the 1st world war, scientists made a huge progress in the field. They invented techniques for detecting TB and they started searching for the chemotherapy. Within 1940s many anti TB drugs like p-aminosalicylic acid (1949) and others came to the market etc. Later some of those were modified to get Isoniazid (1952), Pyrazinamide (1954), Cycloserine (1955), Etheonamide (1956), Ethambutol (1962), Refampim (1963), Refampicin (1967) and others as effective antiTB agents. This discovery surprisingly changed the situation during the World War II. Use of proper medication and intensive health check up reduced the mortality in army. By 1940 the number of TB infected soldiers became only one fifteenth as compared to that documented per year during World War I [31]. Today even 50 years after the discovery of those drugs from the 1950s, a six month course of Rifampicin and Isonazid, supplemented in the initial two months with Pyrazinamide in association with Ethambutol is prescribed as standard treatment for TB with 95% success rate [32].

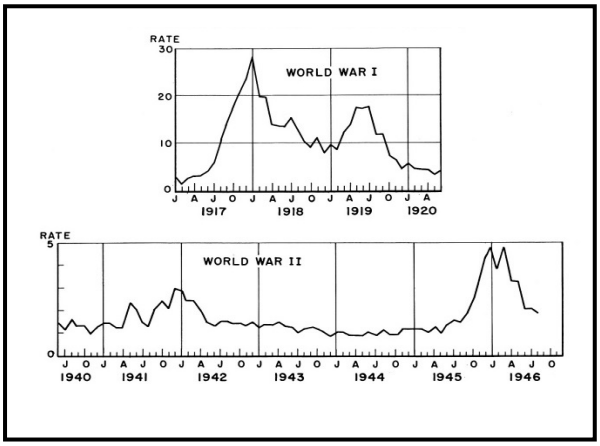

Fig. 4: Comparison between two world wars according to their TB casualties reported.

Development of anti-fungal drug

In 1830 Robert Remak and Johann Schonlein identified fungi to be the etiologic agent responsible for human dermatomycoses but it took around 100 years i.e. until the beginning of the World War to develop effective therapies against it [33].

In old days, anti fungal treatment was limited mainly to ointments like Whitfield's ointment, Castellini's paint, Crystal violet, Undecylenic acid etc.; but they were irritating with minimal affectivity [34]. During World War II soldiers experienced a huge problem due to fungal infections like several kinds of Mycoses, Athlete's foot, Aspergillosis, Candidiasis etc.

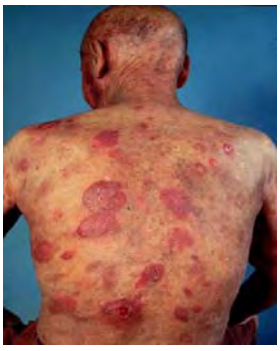

Fig. 5a: Skin mycosis

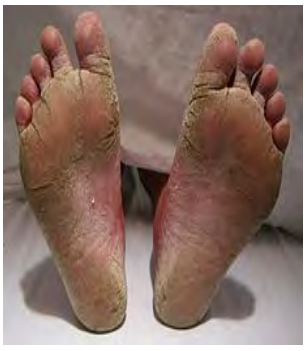

Fig 5b: Athlete's foot

Fig. 5c: Oral candidasis

Their communal bath, inadequate hygiene and sanitation helped in spreading infections and situation was getting tougher day by day. It essentially demanded development of new anti-fungal drugs for getting out of the very trouble.

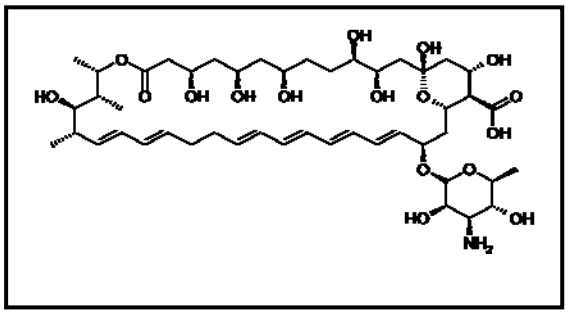

Fig. 6: Nystatin

The intensive study on the field resulted in a few anti-fungal compounds. The main agents belong to the class of Polyenes, Azoles, Ally amines, Benzyl amines etc [35]. Other than these hydroxy pyridone, Selenium Sulphide was also found to have the activity against fungal infection. Just after second world war, within 1950s many drugs like Nystatin (1950), Filipin (1955), Amphotericine-B (1955) etc. came to the market as a result of the social need. Flucytosine (1964), Econazole (1975), Ketoconazole (1976), Itraconazole (1984), Terbinafine (1991) etc. are some of those drugs which later came to the market as antifungal agent.

Development of vaccines

Vaccines are used to treat mainly bacterial and viral infections. The story of vaccination began in 1798, when Dr. Edward Jenner (1749-1823) discovered the technique called “vaccination” and gave a scientific explanation for it. But after that there was a long silence for six decades till the starting of American civil war (1861-1865). During civil war many cases of infectious diseases came to the picture. Approximately 410000 soldiers died of these, which was about 60% of their total casualties. The very situation compelled army authorities to think about the protection of soldiers not only from bullets but diseases too. In this way the initial step was taken by the army research centers towards development of new vaccines. Later Louis Pasteur (1822-1895) and then Maurice Hilleman (1919-2005) played the most important role in developing science for vaccination.

Fig. 7a: Dr. E. Jenner

Fig. 7b: Dr. L. Pasteur

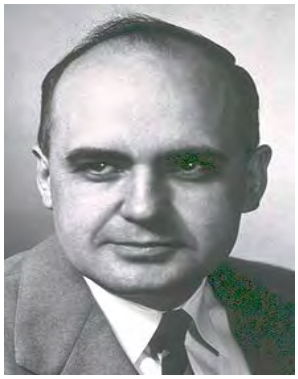

Fig. 7c: Dr. M. Hilleman

At that time there were many common infectious diseases like influenza, typhoid, mumps etc. In the history of wars like in the Civil War military men faced serious problem time and again with infections at battle field or after returning from there. In Canadian war of 1812 around 15000 US soldiers died of diseases like typhoid, pneumonia, measles, smallpox etc [36]. During the American Civil War about 42,000 cases of hepatitis infection were reported, among which 150 led to death [37]. Between 1919 to 1928 there were 25000000 reports of death caused by hepatitis and influenza [38]. Other than these, in 1898 US army troop faced ‘Yellow fever’ along with 20000 reported typhoid cases [39]. So the situation simply accelerated the research related to the treatment of these diseases.

In 1909 first typhoid vaccine was developed at the US army medical school under the supervision of Sir Fredrick Russell [40]. Very soon a few other vaccines also came to the market and their use by the army changed the scenario of the upcoming battlefields. During World War II only 12 cases of tetanus toxoid were reported in the vaccinated US army, whereas a lot of soldiers from the unvaccinated German army died.

Table III: List of vaccines introduced in market during 1880-1970.

Name	Type	Introduced in market	Licensed in US
Cholera vaccine	Bacteria	1879	-
Rabies vaccine	Virus	1885	-
Tetanus toxoid	Bacteria	1890	1914
Typhoid fever vaccine	Bacteria	1896	1914
Plague vaccine	Bacteria	1897	-
Smallpox vaccine(modified)	Virus	1915	1944
BCG vaccine	Bacteria	1921	1927
Diptheria vaccine	Bacteria	1921	1923
Tuberculosis vaccine	Bacteria	1925	-
Pertussis vaccine	Bacteria	1927	1915
Yellow fever vaccine	Virus	1932	1935
Influenza vaccine	Virus	1945	1942
Mumps vaccine	Virus	1948	1967
DTP vaccine	Bacteria	1949	1949
Polio vaccine	Virus	1952	1955
Japanese encephalitis vaccine	Virus	1954	2009
Anthrax vaccine	Bacteria	1954	1970
Measles vaccine	Virus	1963	1963
Rubella vaccine	Virus	1969	1969

Things were going well. But suddenly in 1901, 13 children died when they were injected tetanus contaminated diphtheria vaccine [41]. Again a few days later 9 children died because of tainted smallpox vaccination [42]. As a consequence pharmaceutical companies fell in deep trouble. In 1902 “Biologics Control Act” was propounded to control the quality and the quantity of the medicinal products [43]. Very soon companies as well as their products were taken under license and it started a new era in the pharmaceutical industry.

Table IV: 10 Leading Causes of Death in Sub-Saharan Africa, 2001.

Cause	Percentage of total deaths
HIV/AIDS	19.0
Malaria	10.1
Lower respiratory infections	10.0
Diarrheal diseases	6.6
Perinatal conditions	5.3
Measles	4.1
Cerebrovascular disease	3.3
Ischemic heart disease	3.2
Tuberculosis	2.9
Road traffic accidents	1.8

After 1902 most of the industries started struggling and research on vaccines slowed down. In 1918 the whole world experienced epidemic influenza causing death of millions [44]. As a result attention was again given towards commercial production of vaccines. In 1927 Wolfgang Casper and Oscar Schieman discovered the antigenic property of non-protein substances and this led to the discovery of vaccines for many viral diseases in a safe manner without any microbe contamination [45]. Within 1960 scientists had already discovered 17 of the 25 most important vaccines according to WHO but still in the first decade of the 21st century most number of deaths in many rural areas take place mainly due to HIV-AIDS, Pneumonia, rotavirus infection, Tuberculosis, Measles etc. (From Table IV) [46].

Development of anesthetic and analgesic agents

In earlier days anesthesia was carried out mainly by chloroform or ether. During the Crimean War (1854-1855) and American Civil War (1861-1865) doctors faced many complicated situations during surgery on soldiers wounded in battle field. Chloroform and ether became quite less useful because of their unpredictable anesthetic activities and less selectivity. Though in 1848 John Snow developed an inhaler to regulate the amount of anesthetic agent, it was rarely used by the doctors in the battle field [47]. Again Morphine, which was extensively used as an analgesic agent at that time, was suddenly found to have severe narcotic property. Soldiers who used to take morphine as a pain relief agent became badly addicted of it. At the end of the Civil War there were around 40000 soldiers addicted to Morphine [48]. The effect was so severe that a term 'soldiers' disease' was coined overnight to express morphine addiction [49]. Very soon army authorities realized that morphine can no longer be used in this purpose. This forced them to take step for developing newer anesthetics and analgesic agents.

Some of the analgesics and anesthetics discovered at that time are listed below in Table V and Table VI respectively.

Table V: List of well known analgesics.

Name	Year	Name	Year
Ethyl morphine	1884	Pethidine	1939
Phenyl salicylate	1886	Ketobemidone	1946
Phenacetin	1887	Levorphanol	1948
Diacyl Morphine	1898	Phenylbutazone	1949
Indometacin	1903	Anileridine	1950
Dihydro codein	1908	Kextropropoxyphene	1955
Oxy morphine	1916	Dextromoramide	1956
Pholcodine	1924	Acetaminophen	1956
Hydromorphone	1926	Piritramide	1960
Methadone	1937	Amitriptyline	1960

Table VI: List of well known anesthetics.

Name	Year	Category
Benzocaine	1902	Local anesthetic
Amylocaine	1903	Do
Procaine	1905	Do
Oxymorphone	1914	Intravenous opoid anesthetic agent
Oxycodone	1917	Do
Hydromorphone	1926	Do
Tetracaine	1932	Local anesthetic
Vinyl ether	1933	Inhalational anesthetic
Sodium thiopental	1934	Intravenous non-opoid anesthetic
Methadone	1937	Intravenous opoid anesthetic
Tubocurarine	1942	Muscle relaxant
Lidocaine	1943	Local anesthetic
Flaxedil	1947	Muscle relaxant
Alcuronium	1950	Do
Levorphanol	1950	Intravenous opoid anesthetic
Succinyl cholone	1951	Muscle relaxant
Surital	1953	Intravenous non-opoid anesthetic
Halothane	1956	Inhalational anesthetic
Mepivacaine	1957	Local anesthetics
Pentazocine	1958	Intravenous opoid anesthetic
Prilocaine	1960	Local anesthetics
Methoxyflurane	1960	Inhalational anesthetics

At that time in many cases people used to die in heart attack during surgery. Discovery of efficient anesthetic and analgesic drugs not only removed stress form medical practitioners in battle field but also decreased the fatality rate during any kind of surgery throughout the whole world.

Present situation:

Pharmaceutical revolution had a very prominent impact on society, both from the social and economic point of view. Finally scientists could save millions of life during crisis not being present on the field. But truly speaking 'Industries and Scientists' were not the only contributor in this miraculous triumph. Parallel to their discovery, agenda taken by the Government also played a crucial role in it. In Figure 9 we can see the prominent effect of pharmaceutical revolution in United States. In almost 50 years they amazingly pulled down the rate of death caused by diseases from 21% to only 3.5%. Today, 70 years after the World War II, except a few under developed and developing countries, globally the death rate because of any infection has been dramatically reduced.

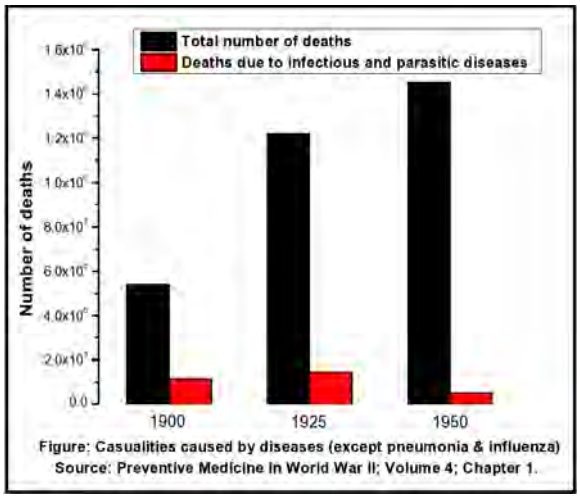

Fig. 8: Result of pharmaceutical revolution in United States

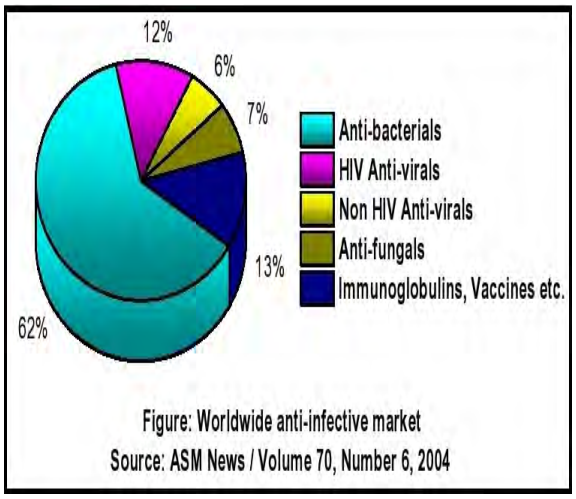

Fig. 9: Worldwide used drugs

Someone quoted "History repeats itself". May be this is the reason behind the endless research in the field of pharmacy. For example, 200 years ago we had no hope to get a way out from Malaria. When the malaria problem was solved, diseases like Tuberculosis came into picture and research was started on it. After a long struggle when the TB problem was solved, Cancer came into the picture and in the same manner HIV, Viral flues etc. and so on. Nowadays we suffer from many diseases like HIV, Typical viral flues for which medication is not known and scientists are working on it. Millions and billions have been invested by both the governments and the private industries and the situation is still the same as it was 200 years before. Simply a repeating history.. a stressful situation with a lot of expectation and crisis.. an endless war against the diseases to get rid of them.

Conclusion

Here we have found the intrinsic relationship between destructive war and constructive science. Now we also know how a war, which takes millions of life, can be a boon for billions of people throughout the whole world. The thing which linked these two up was nothing but the 'Law of mother Nature'. We think of rest when we feel tired, we think of food when we are hungry, we think of freedom when we are bound.. Similarly 'Mother Nature' has taught the whole living system to think about medicines and drugs when life becomes troublesome because of diseases. In this chemical era, the way we treat diseases is completely different from the view point of accuracy and easiness from the rest of the lives in this planet and it has been possible because of the intellect, curiosity, patience and dedication of human being. So, finally the credit goes to us.

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