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CLINICAL TRIALS AND MEDICAL ETHICS

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INTRODUCTION

Medicine has been an important part of the human being. "Health is Wealth" is a motto that is followed by every person in the world. A person can be healthy by eating healthy but some diseases occur which have no relation to what we eat. In earlier times i.e., before the discovery of the allopathic medicines, herbal medicines and Ayurveda was used to cure ailments of the body. But the knowledge of such medicines is long gone and the remaining are not used properly. For diseases like cancer and AIDS, there has been no cure at all if it crosses a certain stage. To extend a person's life, modern medicines are used which have heavy side effects. To test a medicine's effect and its side effects, it needs to be tested and approved. This is where human rights are violated. Not only humans but also animals are abused for the to test drugs and cosmetics. There are laws against such testing on animals and human beings but they are not properly implemented. The experiments which are not approved by the government are conducted illegally and are done by quacks. Such experiments not only result in horrendous pain but also in disability and sometimes death if it is conducted for a long period. This paper deals with such illegal experiments and also the measures taken to save the victims of such experiments.

HISTORY

According to the Bible[2], the first clinical trial was not conducted by a doctor or a physician but by a military leader named *King Nebuchadnezzar (King of Babylon).* He had ordered his subjects to eat only meat and drink only wine. Some people of the royal family had opposed eating meat and thus he let them eat legumes and drink water. After ten days he had observed that the people who ate legumes and drank water were healthier than those who consumed the meat and wine[3].

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[2] "*Book of Daniel" Prologue 1:8-16.*
[3] Collier R. Legumes, lemons and streptomycin: A short history of the clinical trial. CMAJ. 2009;180:23

The first documented medical experiment was conducted by a British physician Dr. James Lind, whom many scientists consider as the father of the clinical trials. In 1747, he had travelled in a British Naval ship, Salisbury and the crew contracted the common problem at sea which is *scurvy*. Dr. Lind had segregated the sailors and had given different types of food to different fragments. All the sailors had similar symptoms such as putrid gums, weakness in knees, spots and lassitude, etc. he had recorded everything in his diary which was mentioned later in his paper, "*Treatise on the Scurvy".*

He had given a different type of food to the sailors. Some were given citrus fruits while some were given few drops of citric acid and the remaining were given seawater, barley, etc. after a point of time when the ship's supplies ran out, he found out that the people who had taken citrus were back on their feet while the remaining were still weak on their knees. This can be accounted for like the first clinical trial to be conducted.

NUREMBERG TRIALS

The Nuremberg trials took place after the World War II. It was to prosecute the war crimes committed by the allied forces during the war. It prosecuted Nazi sympathizers who held major positions in political, military and other areas.

The prosecution took place at the Palace of Justice, Nuremberg.[4] The Nuremberg trial paved a way for the current laws related to military and warfare made by the United Nations and for the establishment of the International Criminal Court. The trials are a collective term for prosecution of 23 members who played a vital role in the Nazi during World War II. The "medical trial" is one of the Nuremberg trials which deals with the gore experiments conducted on the prisoners of war.[5]

The first among the series of Nuremberg trials, the Doctor's Trial had 23 doctors prosecuted for committing crimes against the prisoners of war by conducting medical experiment on them without their consent. It included the soldiers and Jews captured during the war. the experiments were conducted in the *Auschwitz Concentration camp* where the prisoners of war and the Jews were tattooed with different numbers in order to identify their body after their death.

[4] 19th November 1945.
[5] *United States of America vs. Karl Brandt at al" (Case 1) November 21, 1946*

Origin

"Primum non nocere"[6] which is roughly translated as "first do no harm". It is derived from the *Hippocratic Oath* which every doctor has to take and follow during till the end of his profession. According to this oath, doctors are not allowed to harm their patients and should build trust with them. This was not followed properly in the west before World War I, as the medical laws weren't regulated, it led the doctors to perform illegal experiments on patients without their consent.

The first such recorded illegal experiment took place in 1852, where a German physician had injected patients varying from the age group of 17-28, the discharge of a woman affected by syphilis. He had injected the patients to determine the contagiousness of secondary syphilis. The consent of the patients was not taken before this experiment was conducted. The doctor when questioned regarding the ethical aspects of the experiment, passed a statement that the experiment was per the "*Laws of Humanity*[7]*"*. The patients were not informed of this fatal disease and all of them have contacted it. When the ethical basis was questioned, the consideration was given to the principles of the researchers rather than the predicament of the patients.

After effects of Nuremberg Trials

At the end of World War II, military trials were conducted to prosecute the Nazi army for the war crimes that they had committed. The trial bought out the brutal experiments which were conducted by the Nazi physicians on the Jews and the prisoners of war. It reflected the urgent need to create laws that govern the doctors and made sure that such illegal experiments do not take place again. Thus, the trials paved the way for modern medical laws which governed the doctors and made sure that such brutal acts do not happen again.

"The Nuremberg's medical trial gave the biggest contribution to the medical practice which is the doctrine of informed consent for all medical treatment in which the doctor is going to perform an invasive procedure. If the informed consent is not obtained pursuant to the regulations, the patients have the right to sue the doctor for medical malpractice[8]*."*

[6] *book I, sect. 11, trans. Adams, Greek: ἀσκέειν, περὶ τὰ νουσήματα, δύο, ὠφελέειν, ἢ μὴ βλάπτειν*
[7] Ron Rosenbaum, *Explaining Hitler: The Search for the Origin of Evil* (New York: Random House, 1998), p.261.
[8] University of Virginia Health Sciences Centre, student tutorial (2002)

After the trials, the American judges decided to curb such malpractices conducted in the medical profession. Thus, they laid down a set of codes named as "*Nuremberg Codes"*.

The codes are:

1. *Before doctors may perform any experiment on a human being, the voluntary informed consent of subject is absolutely essential.*
2. *The experiment must be based on previous animal testing.*
3. *The experiment must avoid all unnecessary physical and mental suffering and injury.*
4. *The experiment must be conducted by scientifically qualified persons.*[9]

"*The Ethos of modern medicine….is profoundly shaped by the tradition of the Nuremberg".*[10]These codes were formulated not only for doctors but also for those working on pharmaceuticals and research of drugs and cosmetics. These codes have universal application and violation of these codes will lead to prosecution either by compensation or by a trial or sometimes both depending on the harm caused due to the unethical method of experimentation.

The Helsinki Declaration of 1964

Due to the aftereffects of the Nuremberg trials, the *World Medical Association* formulated the *Helsinki Declaration*. This acts as guidelines for the doctors in the field of research and development of drugs.

This declaration was adopted in 1964 and has been amended according to the modern medical standards.[11] if any of the doctors or the researchers were found to have violated any one of these principles, they can be persecuted under the criminal law of that country.

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[9] George J. Annas and Michael A. Grodin, *The Nazi Doctors and the Nuremberg Code(*N.Y.: Oxford university Press, 1992), p. 2:

[10] Vaux, Biomedical Ethic- Morality for the new medicine(New York Harper and Row, 1968) 27.

[11] *The declaration of Helsinki of 1964 are as follows:*

1. *Human subjects should provide voluntary consent and know the risks of participation*
2. *Experimental results must be for the greater good of the society.*
3. *Experimentation should be based on previous animal experimentation.*
4. *Experimentation should avoid unnecessary physical/mental suffering*
5. *No experiments should be conducted if it is believed to cause death/disability*
6. *Benefits must always outweigh the risks*
7. *Adequate facilities should be used to protect subjects*
8. *Experiments should be conducted only by qualified scientists*
9. *Subject should always be at a liberty to stop at any time*

The *Nuremberg Trials* and the *Helsinki Declaration* brought out the importance of Doctrine of Informed Consent.

Doctrine of Informed Consent

According to this doctrine, a person who is going to undergo the experiment, should give consent either orally or by a written consent that he/she is willing to undergo the experiment; provided, the physician or the persons testing the drug gives the patient the information regarding the experiment that he/she is to undergo and the side-effects that will occur during or after the experiment.

The physician should stop the experiment in case, the patient is not willing to continue his treatment anymore or if the physician discovers that the patient would become disabled or that it would lead to his/her death. If the researcher or the physician continues the experiment despite knowing that it will lead to the death or disability, he can be held liable criminally and can be prosecuted under the criminal law of that country.

Case study: Mohr v. Williams[12]

In this case, the plaintiff had approached the physician(defendant) for a surgery of her right ear. The physician had agreed to do the surgery of the right ear. During the examination which takes place before the surgery, the physician noticed that the left ear was in a bad condition than the right ear. the plaintiff was under the anaesthesia and thus the physician did not get the consent of the plaintiff to operate on the left ear of the plaintiff. Thus, he operated on the left ear of the plaintiff without her consent. The operation was successful.

Later the plaintiff sued the physician for damages claiming that she had hearing damages due to the surgery.

The judgement passed that, the consent for operation of the right ear does not give the physician an implied consent to operate on the left ear either. An operation without the consent of a patient is unlawful. It was not a dire circumstance in which the status of the left year was life threatening. Thus, the physician had to pay the damages to the plaintiff.

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10. *Scientists in charge must be prepared to terminate the experiment when experiment when injury, disability, or death is likely to occur.*

[12] 95 Minn. 261, 104 N.W. (12) (1905)

CLINICAL TRIAL

The development of a drug has two stages; preclinical and clinical.

Preclinical trial: the drug is first tested on animals and cell cultures to determine their effects and to test the absorption, distribution, metabolism and excretion and if the drug has accomplished the target.

Clinical trial: the drug after it passes the preclinical trial stage and concludes that there are no major side effects from the intake of the drug, it is later administered to *volunteering* subjects after receiving their informed consent.

Clinical trial is used to research about a particular vaccine or drug or therapy which can be used as potential treatment. It consists of four different phases.

Phase I involves the testing of drugs on a small amount of people who have given informed consent to take part in the clinical trial. In this stage the side effects of the drugs are determined.

Phase II involves testing the drugs on slightly larger number of people who have different body composition. For example; the drug is tested on a person who has high blood sugar or hypertension etc so see whether the drug is effective on such people who have other ailments in the body. This phase is used to determine the efficacy of the drug.

Phase III involves expanding the number of test subjects and it checks the effectiveness of the drug for example checking whether the drug might cause a stroke in the case of antihypertension.

Phase IV show us whether the drug has any long-term side effects and it also involves the post clinical trials result and compounding them to know the effectiveness.

The clinical stages are regulated by the drug regulatory body constituted by a country and they form an ethical committee to make sure that there is no mistreatment of human subjects. The drug regulating authority should give sanction to the drug manufacturers to advertise and sell the drug in the market.

These drugs are usually tested on voluntary patients who are suffering from an ailment and it is usually prescribed by the physicians. These physicians are approached by the drug manufacturing company and they prescribe it to the patients to check whether the drug is

effective as it is tough to find a large number of people who are willing to volunteer for trials. Mostly, drug manufacturing companies seek Contract Research Organisation (CRO) for the purpose of testing the drug. If the drugs are found to be effective, the drug regulatory authority would sanction the release of drugs in the market.

Placebo

In 1863, a physician from United States, *Austin Flint* conducted the first clinical involved the use of placebo. Placebo is a harmless substance which is used on the patients to test their psychological reaction to the experiment. The test subjects are divided into three groups in which one group is administered with the trial drug; the second group is given a placebo and the third group is not administered with any drug. Thus, placebo was an important discovery when it came to experimentation of drugs. The groups are randomized i.e., the participants do not know which group they belong to but they will be voluntary participants who will know the consequences of the experiment.

The first ever randomized experiment was the treatment of *pulmonary tuberculosis*. It was widely publicized and *streptomycin* was the drug on trial. A British statistician named *Austin Bradford Hill* is credited for forming the design for the trial. He can be considered as the *Father of Modern Clinical Trials* as it is his design which is being used currently after some modification.

AIDS Retrovir (AZT)

During the 1980s when HIV/AIDS was running rampant and the people were not able to find a cure for such a virus, a company called as *Burroughs Wellcome* started manufacturing AZT which was the first ever drug to be made for AIDS. It was sold under the brand name *Retrovir*, and after long struggle with U.S. FDA (Food and Drug Administration) for approval, the drug was sent for trials.

This drug trial was the most controversial trial as the drug as it had multiple side effects such as severe nausea, intestinal problems and it also caused damage to the immune system of the test subjects. Thus, to conduct this trial, 300 people who were diagnosed as HIV positive were given the trial drug and a sugar pill (*placebo*) for six months to determine the effects. Neither the patients nor the doctors had any knowledge whether, the patients were given the real drug or a placebo.

After 16 weeks into the trial, the manufacturing company stopped the trial and declared that the drug seemed to be effective in stopping the virus. They had prepared to release the drug into the market saying it would not be ethical if they are stopping such a potential life-saving drug from reaching the people.

After few weeks, some reports floated that the doctors who prescribed the drug weren't informed about the treatment of side-effects which came after consuming the drug. The drug also had questions which were left unanswered. Thus, the people urged the company to release the drug no matter what as they were fine with something that worked against the virus. Another problem surfaced regarding the price of the drug as it was about $8000 per year which was costly at that time for the people to access.

As time passed, the virus level increased and AZT wasn't helping at all because the virus had mutated and had become immune to the drug. The people blamed FDA as they hadn't taken measures to produce any additional drugs to fight HIV. The drugs which were made in the later years gave side-effects such as heart problems, weight issues etc which made the drugs created for battling HIV toxic. But now, AZT is used in therapy for some patients.

UNITED NATIONS CONVENTIONS AND OTHER HUMAN RIGHT LAWS

After the carnage done by the Nazi in the concentration camps during WWII, United Nations and other international humanitarian bodies made sure that such blood shed does not happen again. Thus, they formed laws to prevent exploitation. These laws are applicable globally and a country can use these laws as a basic law for framing their human right codes.

1. **Convention Against Torture and other Inhuman or Degrading Treatment or Punishment (UNCAT) 1984**

This Human Rights treaty aims at prevention of cruel or degrading treatment globally. Before the adoption of this treaty, the UN General Assembly had adopted a declaration in 1975, for the protection of all human beings from cruel and inhumane treatment.[13] Later, the Commission on Human Rights were requested to draft the same which was later signed and ratified in 1984.[14]

[13] *Convention against Torture, and other Cruel, Inhuman or Degrading Treatment or Punishment, 1465 UNTS 85*

[14] Article 1:

2. Customary International Humanitarian Law

The law applies during war and armed conflicts. During World War II, there were no laws to govern illegal pursuits such as experiment on human beings. But after WWII, laws were framed to govern such illegal acts which happens with the prisoners of war.[15]

3. Practice of other International Organizations and Conferences

There have been laws set by the *United Nations*[16] and other *Human Rights* conventions like the one taken in the *Parliamentary Assembly, Council of Europe*[17] and also *International*

Any act by which severe pain or suffering, whether physical or mental, is intentionally inflicted on a person for such purposes as obtaining from him or a third person information or a confession, punishing him for an act he or a third person has committed or is suspected of having committed or intimidating or coercing him or a third person, or for any reason based on discrimination of any kind, when such pain or suffering is inflicted by or at the instigation of or with the consent or acquiescence of a public official or other person acting in official capacity.

[15] *MEDICAL AND RELIGIOUS PERSONNEL AND OBJECTS*

Respect for medical ethics

TREATIES AND OTHER INSTRUMENTS

Treaties

231. *Article 18, third paragraph, GC I provide that "no one may ever be molested or convicted for having nursed the wounded or sick"*

232. *Article 16 AP I provides that:*

1. *Under no circumstance shall any person be punished for carrying out medical activities compatible with medical ethics, regardless of the person benefitting therefrom.*
2. *Persons engaged in medical activities shall not be compelled to perform acts or to carry out work contrary to medical ethics or other medical rules designed for the benefit of the wounded and sick or to the provisions of the Conventions or of this protocol, or to refrain from performing acts or carrying out work required by those rules and provisions.*

Article 16 AP I was adopted by consensus - CDDH Official records, Vol.VI, CDDH/SR.37, 24 May 1977, p.70

[16] ***250.*** *In a resolution adopted in 1989 on the situation of human rights in El Salvador, the UN General Assembly considered that under AP II "no one may be punished for carrying out medical activities compatible with medical ethics, regardless of the circumstances and beneficiaries of such activities" and requested that "medical and health personnel under no circumstances be penalized for carrying out their activities"-*
UN General Assembly, Res. 44/165, 15 Dec 1989, Preamble and sec 5.
251. *In a resolution adopted in 1990 on the situation of Human rights in El Salvador the UN Commission on Human Rights requested the parties to the conflict "in no circumstances to penalize medical and health personnel for carrying out their activities"*
UN Commission on Human Rights, Res, 1990/77, 7 march 1990 sec10.

[17] ***253.*** *In a resolution adopted in 1988 on the protection of humanitarian medical missions, the Parliamentary Assembly of the council of Europe stated that "[medical personnel] may not be punished or molested for having engaged in medical activity, whoever the beneficiaries of such care may be". The Assemble also expressed the*

Covenant on Civil and Political Rights that stands as a universally applicable human rights treaty.

4. Practice of the International Red Cross and Red Crescent Movement (ICRC)

The organization is a combination of other red cross and red crescent societies such as *International Committee, International Federation of Red Cross etc*, that have been put together for helping people who are stuck in the face of disaster, conflict, health and social issues. It is a global humanitarian organization that have put some conventions and laws to make sure that there is no violation of Human Rights.[18]

5. International Covenant on Civil and Political Rights (ICCPR)

The ICCPR was constituted for the purpose of having a human rights declaration that has universal application in contrast to the other non-binding declarations passed. But the framers realized that one single treaty cannot bind the civil and political rights and the social and cultural rights of the people. Thus, two treaties were formed namely ICCPR and ICESCR (International Covenant on Economic Social and Cultural Rights). Both the treaties were signed in 1966 and came into force in 1976. The treaties act as a binding rule in all countries.[19]

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wish the UN draws up a charter for the protection of medical missions. The proposed charter would include, inter alia, the following provisions:

- *[medical personnel may not be punished for having engaged in medical activity*
- *Medical person must scrupulously respect the rules of medical ethics and may not refrain from performing acts required by these rules and*

The assistance must be based purely on medical criteria of a humanitarian kind]. - ***Council of Europe, Parliamentary Assembly, Res 904, 30 June 1988, appendix.***

[18] ***256.*** *To fulfil its task of disseminating IHL, the ICRC has delegates around the world teaching armed and security forces that:*

No person shall be punished for performing medical activities compatible with medical ethics.

Persons engaged in medical activities shall not be compelled:

- *[To perform acts or carry out work contrary to medical ethics; or*
- *To refrain from performing acts or from carrying out work required by medical ethics.]*

-Frederi de Mulinen, Handbook on the Law of War for Armed Forces, ICRC, Geneva, 1987, Sec 217.

- [19] *The right to life*
- *Freedom from torture and inhuman treatment*

CONCLUSION

Nuremberg Trial has been a big eye-opener in the field of crimes related to medicines as cases were not reported in which doctors used patients as lab rats for experimentation. But after the Nuremberg trial, the brutal reality what doctors can do to a potential patient came out to the light. Currently, each country has its medicine laws to govern such illegal experimentation. Though there have been cases where a pharmaceutical company or a quack used drugs on normal patients, there are stringent laws that are used to punish them. If a country doesn't have laws concerning to such crime, it can refer to UN Conventions and other Humanitarian laws.

But currently, there is a lot of procedure to conduct a Clinical trial and only reputed pharmaceutical companies are permitted to do so while it is scrutinized by an ethical committee set up by the government which in turn had reduced the prospect of violation of Human rights. Thus, Clinical trials have evolved as society evolved.