

HUMAN EXPERIMENTATION OF DRUGS*

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-EDITOR]

ABSTRACT

Man has been endeavouring to treat sickness by applying all sorts of means. In the field of human experimentation of drug the name of Chinese God of Medicine stands first. Ballal Sen, king of Bengal gave up death convicts to physicians for experimentation. Scientists like Purkinje and Anton Stoerck experimented upon themselves. In 1796 Hahnemann fully appreciated that in vitro results are not the same in vivo and he recommended experimentation on human body. Mathiolus and Claud Richard experimented on human beings, the effects of Aconite. Experiences of Vincent Bacon, Rodder Moracus and Gmelin are the authorities of Hahnemann in this aspect. Hahnemann termed the method of human testing 'proving' which is the basis for effective and rational therapeutics. Advantages of proving, pros and cons of animal as well as human proving are also discussed.

Always man has endeavoured to treat sickness. He has applied all sorts of means and measures to alleviate the sufferings. The drugs he has drawn from all possible sources. He has also been keen to know more and more about the actions of these drugs in order to effect better results. For this, only living objects could be used. So he tapped the source and experimented his drugs on animals. He has kept his experimentation of drugs on animals to this day.

But if we peep into the past, we find that besides animal experimentation, the drugs have been used on human beings too. Even the experimenters used them on themselves. In this exclusive field of human experimentation of drugs, the name of the Chinese God of medicine, emperor Shen Nung, who is said to have lived about twenty centuries BC stands out first. He could see, according to Chinese tradition, his own

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stomach and see the reactions and observe the effect on his own system of the various medicines he swallowed. Instances are found of criminals whose use was made in such experimentations. Ballal Sen, king of Bengal gave up the death convicts to the physicians to experiment upon. Mathiolus describes that in the year 1561 two robbers were given up to him to experiment upon. John Hunter suggested Jenner, 'why think, why not try an experiment'. He inoculated himself with discharges from venereal patient in order to find out whether gonorrhoea and syphilis were separate illnesses or merely different symptoms of one and the same disease. Through bad luck he inadvertently selected for his inoculation experimentation himself a patient who was suffering from both gonorrhoea and syphilis and as a result of the inoculation he contracted both diseases simultaneously, and developed a syphilitic thickening of the arteries which was ultimately to kill him. Purkinje (1787-1869) a distinguished pharmacologist tested upon himself the action of camphor, belladonna, stramonium and turpentine. Anton Stoeck (1731-1803) made special efforts to increase our knowledge of the use of the drugs. He first experimented upon himself and then administered various medicines in the hospitals. He studied the effect of hemlock, meadow saffron, aconite, stramonium and henbane writing brief and clear monographs about his observations.

In olden times, drugs were administered to sick and their effects were taken as the guiding factor to cure sick.

Albercht von Haller was the first to suggest that if we wish to make ourselves conversant with action of drugs, these drugs must be tested on healthy human body. He made much of testing the action of medicines in healthy persons to find out their physiological effects.

The mighty logician of the Victorian era, John Stuart Mill advocated the deductive method. He said, "If we try experiments on a person in health to ascertain the laws of action of a drug and then reason therefrom how it will act in a particular disease, this may be really effective method and this is deduction". And this precise method was adopted by Hahnemann, the latest in the series of human experimenters, for ascertaining the hidden curative properties of drugs. He was the first to make a thorough study of drugging on the healthy persons by taking them himself and carefully observing their pathogenetic effects. In 1796, Hahnemann published a most important work, entitled "Essay on a New Principle for Ascertaining the Curative Powers of Drugs, with a Few Glances at Those Hitherto Employed". If we seek knowledge on drug actions, chemistry can tell us many things but very cogently pointed out that properties observed 'in the chemical phial' are not the same as in vivo. To find out the action of drugs, experiments on animals are an obvious procedure but by no means adequate, for the body of an animal is not the same as the body of human.

Drugs fatal to humans may produce no effects on animals. Investigators might of course, test drugs on many animals (or animal species) at once, and observe carefully for dangerous effects. But such experiments are at best “rude and awkward” and not in any way “decisive”. Here he was on very solid ground, much more solid, perhaps, than that which supports some current scientific studies. A test tube is not a living body and what occurs in pig or monkey need have no necessary relevance to what occurs in humans.

To lay the basis for rational therapeutics he recommended experimentation directly on humans—healthy humans. Diseased persons, he said, are not suitable subjects for experiment, since diseases can induce various complicating factors, so that even the “greatest practical genius” cannot determine what part is played by the remedy, what part by the disease. Furthermore, medicines to be tested must be used pure and unmixed. The great difficulty is to recognise and identify just what action the drug is exerting. Since objective measurements were at this time not adequately developed, the only reliable indicator was introspective verbal report. This is the basic postulate underlying homoeopathic materia medica; small and subtle physiological effects are all reflected in consciousness, so that merely by observing his own state of consciousness, observer can find and describe all the physiological actions produced by the drug. There is the further implication that what does not appear in consciousness is quite irrelevant, pharmacologically speaking.

Another colossal assumption is implicit in his work, namely, that after injection of a drug whatever appears in consciousness, whatever feelings and sensations the subject experiences, are all casually related to the drug. It is a glorious “post hoc ergo propter hoc”. Today these assumptions appear absurd, but in the eighteenth century they were not unreasonable. They were certainly plausible, considering the state of biological science, and no more ridiculous than many other eighteenth century assumptions.

It is interesting to observe Hahnemann’s acquaintance with the action of medicines was derived from his “written collection” of their peculiar effects. He had spent much time in accumulating the treasures supplied by history which enabled him to select belladonna for the cure of scarlet fever. It was not enough for him that others had recorded and observed the effects of belladonna and other medicinal substances; he was resolved to submit the matter to the test of his own personal experiences. Accordingly four years later, that is in 1805, he published a little work on “The positive affects of medicines; (ie) the effects produced by them in the healthy body”. In this volume are the observations on twenty five substances, most of them powerful vegetable medicines; for example Aco, Bell, Camphor, Digitalis, Hyoscyamus, Hellebore, Nux vomica, Opium, Veratrum and so on.

Enhancing his experiences he studied the history of aconite which has risen from its obscurity and insignificance to its present distinction. In a commentary on Dioscorides published in the year 1598 Mathiolus relates that in the year 1561 two robbers were given up to him to experiment upon. Such was the use then made of criminals. He gave the first robber a drachm of the root but without any result, so he gave a preparation of the leaves, flowers and seed, and in three hours he had the satisfaction of perceiving the most decided effects. There was general lassitude, feebleness, anxiety and a weak pulse. Mathiolus then gave him an antidote upon which he exhibited convulsive movement of the eyes, mouth and head and fell into a faint. Upon this, he had some wine. He then turned on his side and died. Mathiolus gave a similar dose to the other robber, in whom, too, it produced convulsions and great agitation of mind. He recovered however after 7 hours and was probably reserved for further experiment.

The next writer quoted by Hahnemann is Claud Richard. He too tested a drachm of aconite upon a robber and the symptoms were much the same as those observed by Mathiolus.

The next authority is Vincent Bacon. Bacon writes about a case of poisoning with aconite. "On Monday night last, being February the 5th, about ten, I was called in haste to one John Crompter, a silk weaver in Spitalfields. When I came into the room, I found him lying on the bed, his head supported by a bystander, his eyes and teeth fixed, his nose pinched in, his hands, feet, and forehead cold, and all covered with cold sweat; no pulse to be perceived, and his breath so short as scarce to be distinguished. After the administration of sal volatile and some other medicines, he vomitted, and said his head was so heavy that he must needs lie down; his pulse was then a little returned, though very much interrupted and irregular, sometimes beating two or three strokes very quick together, and then making a stop of as long, or a longer time, than the preceding stroke altogether took up. On the following day he was much better, and had been relieved by a sweat. The account he gave of the order of his sufferings after swallowing the aconite, which he had eaten by mistake in a salad was as follows: tingling of the tongue and jaws, sense of looseness of the teeth; this tingling then spread all over the body, especially the extremities; unsteadiness of the joints, particularly of the knees and ankles; twitching of the tendons, with a feeling of interruption of the circulation in the extremities; giddiness, with misty, wandering eyes."

The next is Rodder. He observed pain in the arms and cardialgia, difficult breathing, heat and thirst from aconite introduced into a wound in a man's thumb.

Moracus says how a man ate some of the fresh plant, and soon afterwards became insane. The surgeon who was called in, to show his superior knowledge, ate a quantity of the leaves, and paid the heavy penalty of death for his ignorance and presumption.

Baron Stoerck, who was the first to write a monograph upon aconite, describes the dry leaves as producing an enduring sense of burning, stinging pain on the tongue, and other similar symptoms.

Gmelin is the last of Hahnemann's authorities. All he adds is, "Great prostration of strength".

To this small monograph on aconite, Hahnemann added the affect of substance upon himself. He arranged his observations in a certain order, beginning with the effects upon the head and brain, then passing to those of the face, the organs of sight, hearing and so on, throughout the whole of the body, till he came to the feet; after which he states what he calls its general effects, such as cramps, syncope, fever etc. These effects he denominated symptoms—using this term in a somewhat novel sense.

Expressing his obligation to Hahnemann on the utility of aconite, in subduing the fever of inflammation Prof. Maly wrote in the year 1845: "Dr. Kinderwater says of aconite, that, according to the prevailing ideas, it is contraindicated in inflammatory febrile affections, but that he cannot agree in this opinion, as he has found its utility in various acute diseases. In regard to this observation, while we recommend it to the notice of every physician who has at heart the good of suffering humanity and the art of medicine, we feel ourselves compelled to observe, first, that he did not always employ aconite quite pure (that is, uncombined): second, that he omits all mention of that man to whom we owe the true knowledge and right use of this medicine. It was Hahnemann who first recommended the use of aconite in pure inflammatory fevers with or without eruption, as well as in inflammatory diseases generally in obedience to his principle, *similia similibus*, by which the effusion of blood, except in certain exceptional cases, is wholly obviated. Even were we under no other obligation to Hahnemann, by this single discovery he would, like Jenner, deserve to be ranked among the greatest benefactors of suffering humanity."

As already mentioned, it was destined for Hahnemann to fertilize this method of human testing of drug and to generalise it in laying the basis for effective and rational therapeutics. He termed this method proving in its literal meaning and the subject who tested the medicines, noted and recorded accurately all the "symptoms" resulting from the drug prover.

The requisites of a good prover are that he should be able to recognise the different sensations and variations of function which may occur to him

in average health so that he may not mistake them for effects of the drug during proving.

During a proving, the prover has to avoid the use of medicines, cosmetics and perfumes and should not drift from his usual diet habits. Habits of long standing form the second nature and should not be stopped all at once but can be continued moderately.

The dose should be taken at a time when the prover is in the repose of mind and body. It is better to begin with small dose, gradually increasing it until effects are recognised and to stop taking drug until these effects have ceased appearing. It may then be repeated in somewhat large doses. No permanent illness is produced in this way of proving. The types of symptoms which drugs produce upon the healthy organism may be :

1. Chemical : It depends on chemical affinity which exists between drugs and the tissues of the body and independent of vitality, for example, the burning of the skin by strong nitric acid.

2. Mechanical (or revolutionary) : It consists chiefly in violent efforts on the part of the organism to eject from its cavities the offending substance.

3. Dynamic : It is contingent upon vitality and resulting from the relations of the peculiar properties of drugs to the susceptibilities of the living, healthy organism.

A. Generic : Such as are common to all the members of a certain class of drugs and which serve to distinguish this class from other, but do not furnish means of distinguishing between different individuals of the same class e. g. vomiting and diarrhoea of arsenic, cuprum, varatrum etc.

B Specific : Such as results from the dynamic action of the drug and peculiar to it. They serve to distinguish a given drug from all others.

(i) Central symptoms :—Appear speedily after the drug is taken, are generally the result of comparatively large doses and, in the case of many drugs, are confined to the alimentary canal and to the organs immediately connected with it.

(ii) Peripheral symptoms :— Appear more tardily, are generally the result of comparatively small doses, taken repeatedly or allowed to act without interruption for a long period, and appear in the bones, skin, glands, etc., and in the coordinated phenom of life—often manifestations of dyscrasia or cachexy. Doses which produce central symptoms do not

generally produce the peripheral (or at least not until after a long period has elapsed) and vice versa. For example, mercury, in certain doses, produces well marked and characteristic action upon the alimentary canal and its appendages. In smaller doses it produces, instead of these effects, a series of symptoms in the skin, bones, glands etc—the mercurial cachexy. The former are that we mean central specific dynamic symptoms. The latter are the peripheral symptoms.

Advantages of such a Proving :

1. The changes in health experienced by the physician himself become for him an incontrovertible fact.

2. By such self-observation the physician will himself be trained to be a good observer.

3. The uncertainty about the exact changes in the health of others, produced by a drug, ceases entirely when a physician proves the drug on himself.

4. Experience shows that the organism of the prover becomes, by these frequent attacks on his health, all the more expert in repelling all external influences inimical to his system and all artificial and natural morbidic noxious agents, and becomes more hardened to resist everything of an injurious character by means of these moderate experiments on his own person with medicines. His body resistance against all sorts of infection is increased thereby.

Pros and Cons of Animal Proving :

Cons : (1) The effects of drugs on animals in many cases are different from those on human beings.

(2) Subjective symptoms cannot be studied.

Pros : (1) More violent effects of drugs can be studied.

(2) The result of long-continued employment of drugs in doses sufficient to bring about structural changes without killing, can be studied.

(3) Experiments on lower animals lend themselves to analysis and interpretations and post-mortem study of actual tissue-changes e. g. action of drugs on nerves on blood vessels can be determined and anatomico-pathological study becomes possible.

Pros and Cons of Experiments on Human Beings :**Pros :**

- (1) Subjective symptoms can be studied.

Cons :

- (1) Pathological changes cannot be studied in full.
- (2) Pharmacological action of drugs cannot be studied analytically.
- (3) The result of long-continued administration of drugs in doses sufficient to induce fatal pathological tissue changes cannot be studied. Of course these results are available to some extent in cases of poisoning with drugs either accidentally or wilfully to cause death.

As the proving of drugs on the healthy was an essential factor in Hahnemann's method, he formed a band of provers, that is, of persons volunteering to test drugs on themselves. It included the names of Stapf, Gross, Ruckert, Hornburg, Franz, Wislicensus, Teuthorn, Herrmann, Laughhammer, Hartmann and Hahnemann himself. According to Hartmann, "these, the first pupils and adherents of Hahnemann were bound very closely to the master. No one was ashamed to perform the humblest labour ; the chemical laboratory was a sanctum from which we were as difficult to drive as a fox from his burrow." Gradually various societies and unions of provers were formed to engage in the difficult and important work.

Of the method of proving adopted Hahnemann himself tells us :

"I have the medicine prepared by myself for this purpose in higher or lower dynamizations, in larger or smaller doses, as everyone could take them without being too exhausted...The chief thing was, always to see that the provers should be free from erroneous diet and mode of living, as healthy as possible, and keen to explore the high truths which we are expecting to find, with a strong sense of conscientious honesty, without expecting the slightest worldly advantage, not even to hope for the honour of being publicly mentioned as a 'Prover'.

To meet any contingency arising during the course of proving, Hahnemann made a careful study of antidotes to all the drugs used and kept them handy.

सारांश

औषधियों का मानवों पर प्रयोग

स्व. नन्दराज

मनुष्य बीमारी के उपचार के लिए सभी उपायों के प्रयोग में प्रयत्नशील रहा। औषधी के मानव प्रयोग के क्षेत्र में चीन के चिकित्सा देवता का नाम प्रथम आता है। बंगाल के राजा बल्लाल सेन ने मौत के दोषियों को चिकित्सकों के प्रयोग के लिए छोड़ दिया। पुरकिन्जे तथा अन्टॉन स्टेअर्क जैसे वैज्ञानिकों ने अपने आप पर प्रयोग किया। सन् १७९६ ई में हैनेमन ने पूर्ण रूप से प्रशंसा की कि मानवप्रयोग के परिणाम वे नहीं हैं जो जानवरों के हैं और मानव शरीर पर प्रयोग की सिफारिश की। मेथियोलस और क्लाड रिचर्ड ने अक्रोनैट के परिणामों के लिए मानव पर प्रयोग किए। उस पक्ष में विनसेंट बेकन, रूडर माराकस और ग्मेलिन के अनुभव हैनेमन को आधिकारिक हैं। हैनेमन ने मानव परीक्षण की पद्धति को प्रमाणित करने का नाम दिया है जो कि प्रभावी तथा हेतुबद्ध चिकित्सा विज्ञान का आधार है। प्रमाणित करने के उपयोग, मानवों तथा जानवरों पर प्रमाणित करने के लाभ नष्ट की भी चर्चा की गई।