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Altruism or reckless curiosity? A brief history of self experimentation in medicine

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The history of medicine has, until the last few decades, been an integral part of medical education. In recent years, however, the pressure for curricular time and the increasing emphasis on measurable outcomes and the technical aspects of medical education have led to medical history being deleted entirely from most undergraduate curricula, or being reduced to an elective or optional status.

While it may well be the case that the impact of medical history studies is difficult to define accurately or measure, there are cogent reasons why doctors and medical undergraduates should be cognizant of the history of their profession.

Knowledge of the history of medicine enables one to better comprehend the power, possibilities and limitations of medicine in a contemporary context. By examining even the most mundane parts of contemporary medical life – such as the use of the stethoscope on clinical rounds[1] – one may understand better the social context of medicine, the scientific or philosophical paradigms that underpin clinical practice, and the relevance of language and symbols in medicine. In this way, one can gain an insight into the link between disease, society and the medical profession, and see medicine as intrinsically value-laden and socially constructed.

EXPERIMENTATION IN MEDICINE

Medicine has always been based on evidence, although methods of definition, collation and interpretation have changed enormously over the past two millennia. Over the past century, there has been an increasing demand that medical practice should be based upon 'scientific' evidence derived from well-designed epidemiologic or clinical experimentation. Experimentation itself is not new and has long been a feature of medicine, indeed, both early Greek and Ptolomeic medicine were characterized by an emphasis on empiricism. However, prior to the eighteenth century, experimentation was generally observational and uncontrolled, did not involve an intervention of any significance, involved small numbers (generally one) and was based primarily on animal rather than human research. Where human research occurred it was frequently poorly constructed, was not based on consent and did not consider notions of statistical validity or generalisability. Animal research continues to remain an important feature of medical science and, indeed, most clinical research cannot proceed without prior evidence of appropriate animal studies. However, while animal research or computer modelling may be a necessary precondition for human experimentation, it is generally recognized as an insufficient basis for practice or the introduction of new therapies. Differences between species make extrapolation from one to the other difficult, and this is particularly the case in relation to therapeutics. Penicillin, for example, kills hamsters but not mice, and fiazuridine was demonstrated to be safe in experiments on woodchucks prior to unsuccessful and lethal clinical trials in humans. And yet, experimentation on those species that are biologically most similar to humans (such as chimpanzees) are difficult to defend ethically on logical grounds without reverting to 'speciesism'. Thus, it remains essential to perform experimentation on humans. This confronts researchers with difficult questions regarding *when* to commence the first tests on humans and *on whom* to perform them.

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SELF EXPERIMENTATION IN MEDICINE

The history of medicine is replete with ancient and contemporary examples of doctors who chose themselves to be the first volunteers for research. While some would seek to dismiss 'self experimenters' as members of a lunatic-fringe of science, this is too simple or too dismissive an explanation to explain doctors' desire to be the first volunteer. While examples of self experimentation reveal that some of the doctors or scientists involved in self experimentation were eccentric or were chaotic in either their thinking or their research, many others applied a rigorous scientific method to their own involvement in research. For example, Dr Karl Landsteiner's discovery of the ABO blood-group system in 1900 was based on a methodologically sound analysis of blood samples from six members of his laboratory staff, including himself. (Fortunately the participants included two with blood-group A, two with blood-group B and two with blood-group O!)[2] More recently, the discovery of the link between *Helicobacter pylori* and gastritis in 1984 by the Western Australian scientist, Dr Barry Marshall, was based on a carefully constructed series of self experiments that involved: (i) gastroscopy and biopsy, (ii) ingestion of *H. pylori*, (iii) regastroscopy and biopsy and (iv) subsequent treatment with tinidazole.[3] Both these examples of self experimentation were rigorous; each was valuable and each shed new – and, at the time, unexpected – insights into an area of medicine.

These examples are not unique. Lawrence K. Altman's book, *Who goes first? The story of self experimentation in medicine*, provides numerous examples of self experimentation in a range of areas in medical research.[4] An examination of the history of research into leukaemia, cancer, rabies, malaria vaccines, HIV vaccines, staphylococcal infection, opiates, hookworm, yellow fever, anaesthesia, neuromuscular-blocking drugs, typhoid and scurvy (to name but a few) reveal examples of self experimentation. Among these, a series of self experiments stands out and provides some basis for a better appreciation of the value and limits of self experimentation in medicine.

ANGIOGRAPHY

The heart has always enjoyed respect over and above most other organs in medicine. The heart was long regarded as both the physical and spiritual centre of life and retained its power and mystique until this century. While doctors could let blood, purge, or apply any range of poultices, the heart itself remained hidden. It could not be touched or seen. It took the self experimentation of a young German doctor, Werner Forssmann, in 1929, to begin the process of making the heart both visible and accessible. Forssmann was a young and enthusiastic internist who was apprentice to Dr Richard Schneider. He had previously seen sketches of French physiologists accessing a horse's heart via its jugular vein and was impressed that this gave some understanding of the physiology of the heart without causing morbidity or mortality.[5] Forssmann asked himself whether the same technique could be applied to humans and whether this would provide some route of access for giving fluids and drugs. He approached Dr Schneider with his idea and asked whether he would allow Forssmann to perform similar experiments on dying patients or, alternatively, on himself. His request was refused by Schneider. At this point Forssmann decided that he would not be deterred in his desire to follow his idea through. He felt sure that he could access the heart by passing a flexible tube of sufficient length through a peripheral vein into the right atrium. To do so, Forssmann required sterile surgical equipment and a ureteric catheter. This equipment was kept locked in the operating theatre under the supervision of a senior nurse named Gerda Ditzen. To gain her cooperation, Forssmann spent considerable time discussing medicine, therapeutics and cardiac physiology, lent her text books and shared his excitement for medicine with her. Ditzen was soon enthused and, when Forssmann eventually broached his idea for cardiac catheterization with her, she agreed not only to provide him with the surgical equipment, but also to be the first volunteer!

So it was, one evening, that Forssmann obtained all the necessary equipment and assisted Ditzen on to a surgical table so that he could prepare her for catheterization of her brachial vein. She did not object to his loosely tying her arms to assist him in preparation. What Ditzen was unaware of was that Forssmann was always intending that he himself should be the initial volunteer. Thus, while Ditzen lay patiently on the surgical table awaiting his reappearance, Forssmann incised his brachial vein and passed the ureteric catheter into his forearm. He was able to advance the catheter with nothing more than a burning sensation until such time as he felt it was likely to be in his heart. At this point Forssmann required some proof of his experiment and so sought radiographic evidence. For this he needed Ditzen's assistance. He declared what he had done to a furious Ditzen and then, with her assistance, made his way downstairs to the radiography department. Unfortunately, at this

time the radiographer alerted one of Forssmann's comrades, who angrily attempted to remove the ureteric catheter from his arm and terminate the experiment. In the end, however, he relented and Forssmann was able to gain some radiographic evidence of the catheter in his right atrium. Forssmann was to repeat his experiment on a number of occasions, both before and after publication of his experiences in *Klinische Wochenscrift*.[6] He also went on to perform angio-cardiography using sodium iodide on dogs and on himself. Forssmann only ceased self experimentation following painful and unsuccessful aortography. By the time of his 'retirement' there could be little doubt that Forssmann's work had clearly advanced the fields of cardiology, therapeutics and medical imaging.

THROMBOCYTOPENIA

Blood has always fascinated doctors and medical scientists. In Eastern and Western medicine, blood was seen as a critical life-force and blood-letting was the dominant therapy in medicine for over 2000 years. While pathophysiology, cellular biology and molecular medicine eventually led to the demise of blood-letting in the eighteenth and nineteenth centuries, the fascination with blood and the diseases of blood has remained.

On a balmy April night in 1945, a 17-year-old girl was admitted to Cambridge City Hospital in Boston, USA, with vaginal bleeding. The medical officer on duty made a hasty diagnosis of an unsuccessful abortion and brusquely presented this diagnosis to the young girl and her shocked parents. However, full blood count subsequently revealed severe thrombocytopenia. A diagnosis of idiopathic thrombocytopenic purpura (ITP) was made and she proceeded to splenectomy. Unfortunately, the young girl died of postoperative bleeding related not to thrombocytopenia but to a poorly applied splenic artery ligature.

This entire episode was observed by a young internist by the name of William J. Harrington. He was horrified by the manner in which the girl was treated, the missed diagnosis and her iaterogenic death, and decided to pursue an interest in haematology. Harrington applied for and won a National Institute of Health grant, which he shared with Dr James Hollingsworth, enabling both to work with Dr Carl Moore. The cause of ITP was unknown at this stage, although it was known to cause easy bleeding and bruising and to be responsive to splenectomy and steroids. Working together, Harrington and Hollingworth noted that children of mothers with ITP were frequently thrombocytopenic at birth. To the two researchers, this suggested that there was a plasma component that crossed the placenta and destroyed the baby's platelets *in utero*. The question was, therefore, whether they could prove that there was a substance in plasma that could cause thrombocytopenia. Unfortunately, animals were not known to experience ITP and so the researchers realized that they would need a human model to test their hypothesis. Harrington thought he could determine the basis of ITP by taking plasma from a patient with ITP, injecting it into another person who did not have the condition and then measuring their platelet count. All they needed was a co-operative patient with ITP.

They did not have to wait long. Shortly thereafter a middle-aged woman with persistent thrombocytopenia postsplenectomy was admitted with bleeding. When told of the experiment, she enthusiastically consented to the researcher's request. Serology found that her blood group was O-positive. This was the same as Harrington's blood group, so Harrington was to be the first volunteer.

The researchers quickly organized an exchange transfusion of approximately 250 mL of blood between the patient and Harrington. Prior to the exchange transfusion the patient's platelet count was measured at 5×10^9/L and Harrington's was measured at 250×10^9/L. Harrington also underwent a bone marrow biopsy to demonstrate normal megakaryopoiesis. The exchange transfusion itself proceeded without complication. However, shortly after the transfusion, Harrington experienced a generalized seizure in the laboratory. He recovered spontaneously from this and proceeded to assist Hollingsworth with morphological examination of the patient's and his own peripheral blood! Post-transfusion platelet count confirmed the researchers' suspicions. The patient's platelet count was not significantly different at 6×10^9/L, whereas Harrington's had fallen dramatically to 10×10^9/L. The researchers were elated; however, their elation was tempered during Dr Moore's clinical round the following day when Moore (without realizing what had transpired) suggested that the patient who had participated in their research was likely to have terminal ITP because she had not responded either to steroids or to splenectomy. This caused Harrington to reflect on the exchange transfusion that he had just had from this patient and, as a result of this, the men shared their secret experiment with Moore. Dr Moore was disturbed by their actions but supportive, nonetheless.

Over the following 3 days, Harrington experienced a series of complications related to progressive thrombocytopenia including: (i) mucosal and cutaneous petechiae, (ii) gingival bleeding, (iii) epistaxis and (iv) rectal bleeding. In an effort to avoid intracerebral haemorrhage, Harrington slept upright, supported by pillows, as a means for reducing intracerebral pressure. He also did his best to avoid the attention of medical students who aggressively sought him out to examine his abdomen for evidence of splenomegaly!

Within a week, Harrington's platelet count had recovered and he was able to return to normal work. He was to try his experiment a further 35 times with differing amounts of plasma to examine for evidence of a dose effect. He was not alone: Hollingsworth and Moore also participated in similar self experiments, as did a series of other colleagues, including laboratory staff, technical staff and secretarial staff. Fortunately there were no deaths, no intracerebral events, and none of the self experimenters developed chronic ITP.

The importance of this research cannot be overstated. The research team established the immune basis of ITP and provided clear evidence for the existence of autoimmunity.[7] Hollingsworth's work on antiplatelet antibodies also formed the basis of subsequent work by Professor Jean Dausset into antiplatelet antibodies and the human leucocyte-associated antigen system.

THE VALUE AND LIMITATIONS OF SELF EXPERIMENTATION

The experiments of Forssmann and Harrington bear all the hallmarks of other episodes of self experimentation. Each had a deep curiosity in science; each desired first-hand experience of research; each was driven by a spirit of adventure; and each was certain that using themselves as research volunteers would increase the validity and dependability of their research. The extent to which their actions were driven by necessity, convenience or a desire to share risks with other volunteers is uncertain. The reasons why doctors would choose to experiment on themselves are often unclear. They may be driven by an altruistic desire to accept the same risk that they would ask of other volunteers of research; they may be driven by a concern of the inequity of the participation of some subjects, such as prisoners, in research; they may seek to avoid the bureaucratic 'red tape' of scientific or ethics review; they may seek fame, fortune and academic advancement from rapid scientific progress; or, more likely, they may be driven by an insatiable scientific curiosity and a need to participate closely in their own research.

There are clearly significant flaws in the entire notion of self experimentation. There are substantial difficulties with scientific validity and generalisation because there is generally only one subject. The participation of the researcher in the experiment would also appear to make the research less objective and the results more open to questionable interpretation. Self experimentation would also appear to provide a context in which researchers would take unnecessary risks or risks that they would otherwise find unacceptable in research.

Despite this, self experimentation raises important considerations about the manner in which researchers structure human experiments and the questions that they expect such research to answer. Self experimentation also asks us to consider the value that we attach to altruism and to human beings in general, and whether the lives of patients or research subjects are implicitly devalued against the lives of doctors or scientists.

Altman suggests that the question of self experimentation should be considered by all researchers.[4] He suggests that researchers should ask themselves, or be asked by ethics committees, whether they would be prepared to have the research carried out on themselves and if not, why not. This would appear to be a valuable and important question for no other reason than that it forces doctors and researchers to examine more closely the notion of risk and the concept of consent in research. I would also suggest that this issue raises another question for researchers: to what extent have they ever participated in research as a subject, rather than as an experimenter. Many doctors have never been sick. The majority have never and will never experience difficulty in access to health care and will never know what it is like to be disempowered within the health-care structure. Many have also never been in the position of not understanding the situation in which they find themselves. Many have never participated in research, nor have been asked to participate in research. While this is not an argument for self experimentation, it is certainly an argument for empathy and for active participation in the research endeavour as a subject as well as a researcher.

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