# MEDICINES DEVELOPED WITHOUT ANIMAL EXPERIMENTS AND TESTING RESEARCH

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***Alternatives to animal testing experiments***

If animal experiments correctly mimicked human disease and gave an accurate impression of our response to drugs, there would never be any need for studies with patients or clinical trials. But with most animal models of human illness either poor or non-existent,[1] it is not surprising that key advances in the understanding and treatment of disease often come not by experimenting on animals but from direct studies of people.

Human studies can take a variety of forms: while epidemiology requires an investigation of both sick and healthy *groups* of people, forming the basis of preventive health care, clinical observations are carried out on individual patients, often at the bedside. Doctors record case histories, measure blood pressure, take tissue and urine samples for analysis, and use modern scanning techniques such as positron emission tomography and magnetic resonance imaging to discover what is happening in the body. The resulting picture of disease provides a rational basis on which to devise treatments. Further vital information comes from autopsy findings and studies with healthy volunteers. Medical science also has a rich and productive history of researchers carrying out experiments on themselves.

The importance of human studies is stressed by Dr Paul Beeson of the Veterans Administration Medical Center in Seattle, who writes,[2] "progress by the study of man is by no means unusual, it is more nearly the rule, "Clinical researchers like Beeson argue that advances in the understanding and treatment of human disease must at least begin, and

end, with studies of people.[3] To begin with, clinical observations are necessary to characterize the disease so that even if animal experiments are contemplated, scientists know which symptoms have to be induced. And ultimately, any findings that arise from animal research must be confirmed or rejected in human trials. Because the development of an animal model requires prior knowledge of the human condition, it is very difficult for such animal experiments to generate major insights.[5]

Fortunately, although many scientists *do* resort to animal experiments during this central phase of investigation, others focus on further clinical and epidemiological studies, tests with healthy volunteers and laboratory research with human cells and tissues. The proof that animal experiments are not "essential" comes not only from recorded contributions of clinical research but more obviously from those diseases for which medicine has been forced to rely on human-based research because there is *no* animal model. For instance, the inflammatory diseases of the intestine - Crohns disease and ulcerative colitis - have no animal counterparts and consequently the delineation of their clinical features, their diagnosis and their treatment have all been achieved by clinical investigation during the past half-century.[4]

Another example is yellow fever.[6] No animal was known to be susceptible when, in 1900, Dr Walter Reed, head of an American military team to Cuba, proved through experiments on human volunteers that mosquitoes did indeed transmit the disease. Reed's findings were put to good use in Havana where improved sanitation and quarantine not only wiped out yellow fever but almost completely rid the area of malaria, another mosquito-borne disease.

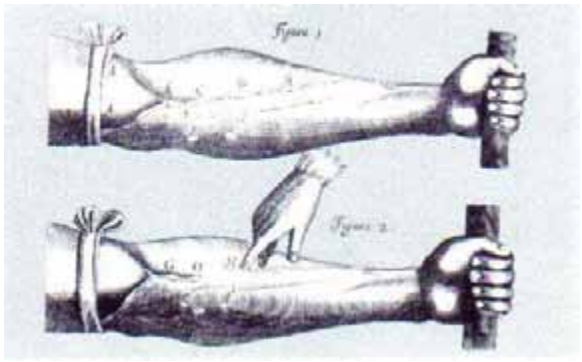
It is true that compared with the use of animals, which scientists regard as disposable, clinical research does require more skill, time and patience to avoid unnecessary risks to participants. However, there are important advantages. Not only are clinical studies directly relevant to

human disease but the everyday practice of medicine, in which doctors make observations and evaluate treatment in millions of patients, carries with it a huge potential for deriving knowledge that cannot be developed in any other way.[4]

Happily, a glimpse at just some of the main areas of medical science is enough to show the vital contribution of clinical research* and dispel the suggestion that all advances have relied on animal experiments.

**Physiology and how the body works**

An understanding of how the body functions has always been a central objective of biomedical research. Many physiologists use animals for the purpose, a common procedure being to damage or interfere with a part of the body to see how it affects another. But since there are almost unlimited and varied cases of human illness and injury, an effective alternative would be to take advantage of these "experiments



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►***Harvey's famous experiment on the forearm which illustrated the circulation of the blood.***
*No blood flows through valve O towards the wrist after blood is pushed away from segment OH. When the finger is removed from point H, blood flows from H to O*

of nature" and make careful observations and deductions. The famous physiologist William Harvey recognized this as long ago as the 17th century when he wrote,[7] "Nature is nowhere accustomed more openly to display her secret mysteries than in cases where she shows traces of her workings apart from the beaten path; nor is there any better way to advance the proper practice of medicine than to give our minds to the discovery of the usual law of nature, by careful investigation of cases of

**The achievements of epidemiology and human issue studies are examined in the essays People Power - The Achievements of Epidemiology over Animal Methods* and *Human Tissue - A Neglected Experimental Resource* both written by Dr Robert Sharpe and part of the **In Focus** scientific series

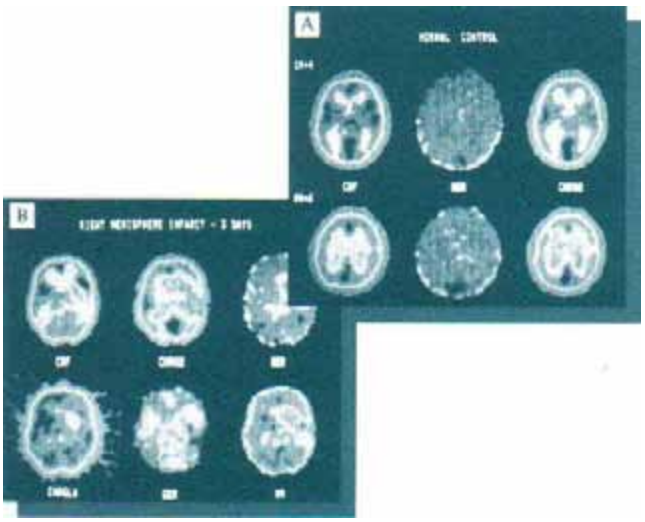
rarer forms of disease." In any case, human studies would still be necessary to validate the results of physiological experiments on animals, assuming they were intended to have any medical relevance.

A famous case is the early study of stomach physiology by the American military surgeon William Beaumont.[8] In the 1820s, Alexis St. Martin, a young Canadian trapper, received a gunshot wound in the abdomen and thus came under Beaumont's care. Although the wounded man eventually recovered, he was left with a gastric fistula and through this artificial opening Beaumont was able to observe the walls of his patient's stomach and obtain pure gastric juice. For two years the patient and surgeon became partners in a valuable piece of physiological research with Beaumont making almost daily observations and experiments. Chemical analysis showed that the gastric juice contained free hydrochloric acid and was only secreted when food entered the stomach. Beaumont demonstrated the action of gastric juice both within the body and in the test tube, and carefully noted the changes in stomach physiology as a result of fear and anger, feverish symptoms and excessive alcohol intake. Ultimately, Dr Beaumont worked out over 50 positive conclusions and according to Sir Arthur Hurst,[9] Senior Physician to Guy's Hospital in London, his research "…laid the foundation of our knowledge of gastric digestion."

Another example is the study of brain function. Although many researchers rely on animals with deliberately induced brain damage, neurologists Antonio and Hanna Damasio at the University of Iowa College of Medicine observe patients with brain injuries and relate changes in their behavior to the damaged part of the brain.[10] The Damasios have studied brain lesions in 1500 patients, often locating injuries in living subjects with the use of imaging techniques. The impetus to such studies, and the realization that different activities are located in different parts of the brain, stemmed from the clinical observations of Paul Broca during the 1860s when he identified the speech center.[4,11] Broca found that patients with left frontal lesions of the

brain also suffered speech impairments. More recently, it was clinical investigation of patients with amnesia that pinpointed the hippocampus as the crucial brain structure involved in memory.[10]

The examination of patients with deficiencies in their immune systems provides important clues to our understanding of the body's natural resistance to disease. According to immunologist Robert Good,[12] the discovery of agammaglobulinemia in 1952, a rare condition in which there is no gamma-globulin in the blood, leaving patients susceptible to infection because they are unable to form antibodies, "provided a new and clear cut opportunity to gain insight into the nature and significance of the immune response in man." Good referred to his studies as "experiments of nature."



Images from Medical Research Council Cyclotron Unit (UK)

► ***Tomographic Brain Scans:*** *These images enable researchers to build an accurate picture of disease processes as they occur in the* ***human*** *patient. Scan A depicts a normal scan while scan B shows brain damage after a stroke.*

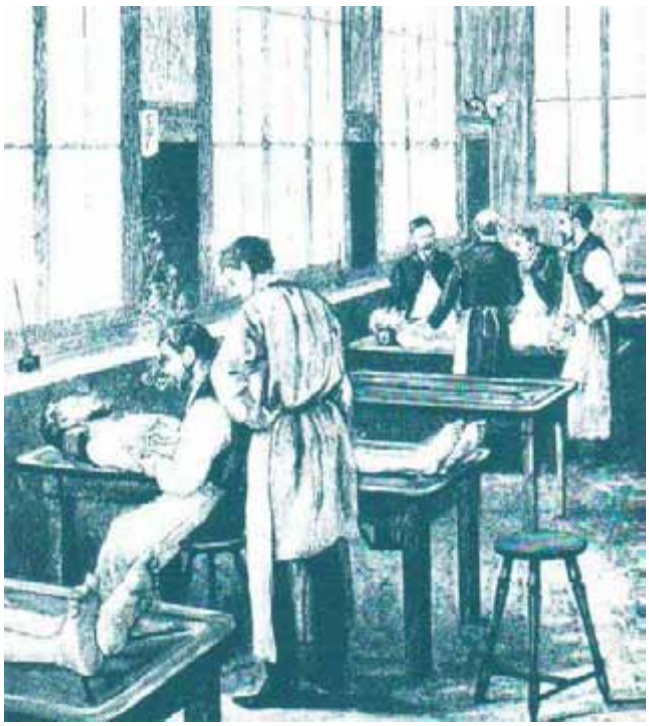
Human physiological studies are not restricted to cases of illness. The same scanning techniques which permit the investigation of disease in living subjects, are also being applied to physiological studies of healthy volunteers. For instance, nuclear magnetic resonance spectroscopy is being used to study muscle physiology.[13] There are also new ways of investigating brain functions: the techniques involve electrical or magnetic stimulation of nerve cells through the intact skull of healthy subjects.[11] In the past, such studies were performed by inserting small electrodes into the brains of patients during therapeutic

neurosurgery.

**Drug Research / Herbalism**

The oldest and most widely practiced form of medicine in the world is herbalism - the use of herbs and plants to treat disease. Research by herbal doctors and manufacturers relies on long established use and experience in practice: knowledge accumulated during past generations means that history has been one long clinical trial! Important examples of plant-derived medicines include the powerful painkiller morphine (from poppies), the antimalarial drug quinine (from the bark of the cinchona tree), the muscle relaxing agent curare (from the wourali root used by the Incas to paralyze their prey), and the antileukemia drug vincristine (from the rose periwinkle plant *vinca rosea).* Today, plants provide us with a quarter of our medicines.[14]

An analysis of some of the main drugs used to treat cancer and heart disease, the principal causes of death in Western society, provides further evidence for the contribution of clinical investigation. For



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► *Post-mortem studies first linked diabetes with a damaged pancreas and also revealed a vital chemical imbalance in the brains of patients with Parkinson's disease. Despite their important contribution to the understanding of human disease, autopsy studies are declining.*

instance, most of the main classes of anticancer agents - the alkylating drugs, the antimetabolites, the antitumor antibiotics and hormonal drugs - were all developed from clues derived during human studies.[15] According to Dr Irwin Bross,[16] formerly of the Roswell Park Memorial Institute for Cancer Research in New York, "practically all the chemotherapeutic agents which are of value in the treatment of human cancer were found in a clinical context rather than in animal studies."

The alkylating agents were the first drugs to be developed which killed cancer cells. John Cairns explains[17] how they "originated with the observation that one of the long term effects of the mustard gases used in WW1 was damage to the bone marrow." Doctors noticed that exposed soldiers and workers experienced a dramatic lowering of their white blood cell count and suggested the chemicals as a possible treatment for leukemia and lymphoma - cancers characterized by an overproduction of white blood cells. In his book *Cytotoxic Drugs in the Treatment of Cancer* (1969), E. Boesen describes how "the nitrogen mustards were themselves originally submitted for clinical trial as a result of studies that had been made of their toxic effects in man. They were not discovered by any test system." The comparative success of the (still used) nitrogen mustards provided the incentive to develop further alkylating agents.

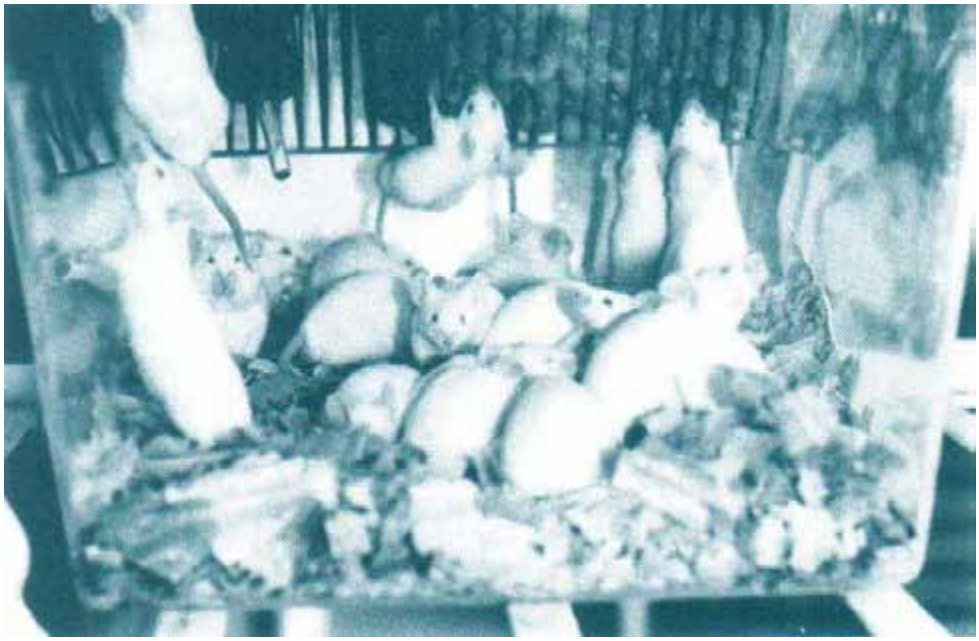
Another example is the corticosteroid drugs. With cortisone modifying the signs and symptoms of so many diseases, it was natural that it would be tried in cancer patients. Only later was it tested on animal tumors.[18] Nevertheless, there were clues from clinical studies of Cushing's Syndrome that suggested cortisone would be effective against human cancer. Cushing's Syndrome is characterized by excessive production of cortisone from the adrenal gland leading to a decrease in some body tissues including muscle wastage. Cortisone's action on muscle tissue suggested that it could also be effective against *cancer* tissue. The success of cortisone led to the development of closely related steroids such as prednisone, a very useful drug despite proving

useless against a variety of animal cancers.[19]

The development of methotrexate, a widely used drug for the treatment of leukemia and other cancers, is a further triumph of the clinical method. Methotrexate belongs to a class of drugs known as folic acid antagonists, whose therapeutic potential was discovered by Farber during his attempts to treat leukemia.[20] Researchers had shown that folic acid, a member of the vitamin B complex, inhibited the growth of tumors in mice and, although the effect could not be confirmed in other laboratories, Farber nevertheless decided to test the drug in clinical trials. But contrary to the original animal experiments, folic acid actually made the leukemia worse! Farber reasoned that the desired effect might still be achieved by using drugs - "antagonists" - that blocked or opposed the action of folic acid.

The idea was to choose antagonists which so resembled the folic acid that cancer cells would be fooled into believing that they were the vitamin necessary for growth, when in fact they had no nutritional value at all. On the contrary, the antagonists would prevent the folic acid from reaching the cell, which would then be unable to grow. Without any

▼ The *laboratory mouse is cheap and commonly used in cancer research, but the data produced is often inapplicable to the human disease.*



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preceding animal experiments, Farber tested a variety of folic acid antagonists on children with leukaemia, an illness whose prognosis had hitherto been grim. The results were very encouraging and provided the incentive to develop further antagonists, including Methotrexate.

The success of the folic acid antagonists proved that it was possible to block the growth of cancer cells, and antagonists were subsequently developed to inhibit the action of other cell nutrients such as the purines. Scientists call this the "antimetabolite" approach.

The substantial improvement in survival for some of the rarer forms of cancer, especially childhood leukemia and Hodgkin's disease, again depends on clinical research. Treatment depends on using a combination of agents which, together, have an improved effect over individual drugs. In his book *Principles of Cancer Treatment* (1982), Dr Steven Carter describes how many effective drug combinations emerged by trial and error in human studies and not because they were predicted to work by animal tests. It could hardly have been otherwise, because, as Carter explains, "while much work has been done testing drug combinations in rodent tumors, no system with established predictability has been illuminated."

Clinical research has also played a key role in developing heart drugs. The use of digitalis as a heart stimulant has a long history and derives from folklore reports that the foxglove plant could cure "dropsy." In 1775, the English physician William Withering commenced a long series of trials using digitalis extracted from the plant.[21] He believed the only way to test the efficacy of herbs was to administer them to the sick. Withering proved the value of digitalis in treating dropsy, which was later shown to be a symptom of heart failure. In 1905 further clinical studies showed that digitalis could also be used to treat atrial fibrillation,[22] a condition in which the heart beats in an irregular and chaotic fashion. Nowadays, doctors rely on digitoxin and digoxin, pure substances extracted from digitalis but which perform the same function. They are

still regarded as amongst the most valuable drugs for heart failure.

Quinidine is another heart drug originating purely from clinical investigation. Quinidine is closely related to quinine and both alkaloids come from the cinchona bark, a substance introduced from Peru in 1638 for the treatment of malaria and used by Jean-Baptiste de Senec in 1749 for palpitations. Heart specialist Vaughan Williams takes up the story :[23]

***"Before the first world war Wenckebach was consulted by a patient in whom atrial fibrillation was diagnosed. Since there was no remedy for the disease, Wenckebach reassured his client that his condition was compatible with many more years of fruitful life and saw him on his way. The patient declined to be reassured, however, promised to return the following day, and vowed that his fibrillation would have stopped. He did, and it had. Wenckebach walked over to lock the door, and placing the key in his pocket, said 'You do not leave this room until you have told me how you did that.' It transpired that his client was a merchant whose business took him to parts of the world where malaria was endemic and he was accustomed to take quinine. He had noticed that his fibrillation was sometimes arrested after a large dose."***

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► *The discovery of Antabuse, used as a form of aversion therapy for alcoholics, originated with the chance observation that the drug produces unpleasant symptoms after consumption of even a little alcohol. Researchers from the Danish pharmaceutical company Medicinalco had been carrying out experiments on themselves to test the drug as a possible treatment for parasites.*

But quinine was not always successful and in 1918, four years after Wenckebach's report, Frey compared the effects of quinine, quinidine and cinchonine in patients with atrial fibrillation.[24] Quinidine proved by far the most successful and to this day remains an important treatment for cardiac arrhythmias.

The value of lignocaine and phenytoin as antiarrhythmic drugs was discovered mainly by chance after their introduction for other purposes:[27] the local anesthetic lignocaine was shown to have antiarrhythmic properties during cardiac catheterization of patients,[25] while phenytoin's effects on the heart were first observed during its clinical trial for epilepsy.[26]

Nitroglycerine (or glyceryl trinitrate) is still considered one of the most effective remedies for the pain of angina even though it was developed over a hundred years ago. During the 1870s, the young London physician William Murrell became interested in a current medical controversy about the effects of nitroglycerin, which some doctors thought might be useful to treat spasms and nervous disorders. Murrell decided to make up his own mind and tested the drug on himself.[6] He noticed that its actions were similar to those of amyl nitrite, a treatment for angina. Murrell argued that nitroglycerin could also be valuable for the same condition, a conclusion that has stood the test of time.

The quinidine story illustrates an important therapeutic principle - that an alert physician can discover important new uses for drugs originally introduced for an entirely different purpose. Examples include new treatments for depression, epilepsy, schizophrenia and Parkinson's Disease.[27] In addition, three of the four major classes of drugs used to treat high blood pressure were not known to have this effect until after they were given to patients for other conditions.[4] For instance, the beta-blocking drug propranolol was first marketed for treating cardiac arrhythmias, and then angina, but was soon found to lower blood pressure in patients, an unexpected discovery.[27] This observation led to

the use of beta-blockers as one of the major treatments for high blood pressure.

Another example is the discovery of drugs to suppress the body's natural defense mechanisms, a key factor in the development of organ transplantation. Apart from cyclosporin, the main drugs used in transplant surgery (the antipurines and the corticosteroids) are also anticancer agents whose notorious side effect is to suppress the immune system.[28] Indeed, most of the commonly used anticancer drugs were subsequently found to be immunosuppressive.[29]

**Anesthesia and Self-Experimentation History**

One of the most important advances in medical history was the discovery of anesthetics. In fact, patients waiting for the 'terrifying ordeal of surgery in pre-anesthetic days would no doubt say it was *the* most important! Perhaps more than any other field, the development of both general and local anesthetics owes an enormous debt to the physicians and scientists who experimented on themselves.

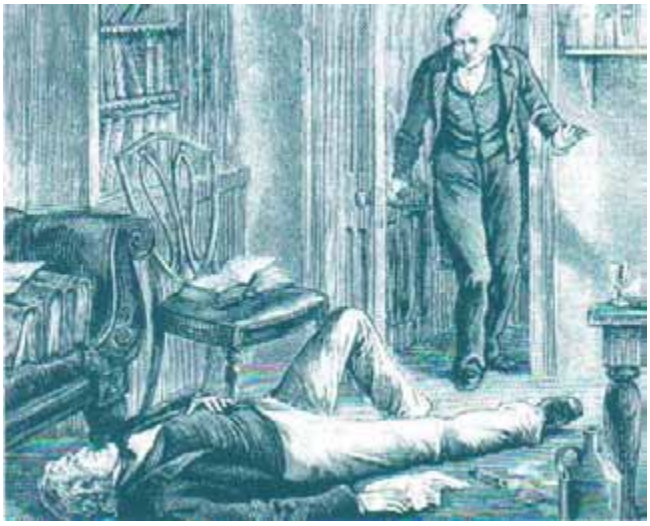
In 1800, Humphrey Davy inhaled nitrous oxide, or "laughing gas," and noted that it eased the pain of an inflamed gum. He suggested its use in surgical operations but inhaling laughing gas was a kind of parlour game and the proposal was ignored. By the 1840s "ether frolics" and laughing gas parties were popular entertainments and it was his experience while inhaling ether that first prompted Dr Crawford Long to suggest its use during surgical operations.[30]

After inhaling ether, Long observed that neither he nor his colleagues had any recollection of what would normally have been painful experiences. In 1842, Long put his theory to the test and successfully removed a tumor from the neck of a friend.[31] There was no pain. In 1844, Horace Wells, a dental surgeon, persuaded one colleague to give him nitrous oxide while another extracted a tooth.

The news of ether spread rapidly and encouraged Edinburgh gynaecologist James Simpson to investigate other vapors that might also have anesthetic properties. Professor Miller, one of Simpson's colleagues, describes how the anesthetic properties of chloroform were discovered:[8]

***"Late one evening - it was the 4th of November 1847 - on returning home after a very weary day's work, Dr Simpson, with his two friends and assistants, Drs Keith and Duncan, sat down to their somewhat hazardous work in Dr Simpson's dining room. Having inhaled several substances, but without much effect, it occurred to Dr Simpson to try a ponderous material which he had formerly set aside on a lumber table, and which on account of its great weight, he had hitherto regarded as of no likelihood whatever.*** **That** ***happened to be a small bottle of chloroform. It was searched for and recovered from beneath a heap of waste paper. And with each tumbler newly charged the inhalers resumed their vocation. Immediately an unwanted hilarity seized the party; they became bright-eyed, very happy and very loquacious - expatiating on the delicious aroma of the new fluid ...a moment more and then all was quiet - and then*** **crash.** ***The inhaling party slipped off their chairs and flopped onto the floor unconscious."***

Within a fortnight Simpson had administered chloroform to at least 50 of his patients with excellent results.



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► *A colleague discovers a prostrate Dr Simpson after an inhaling session. Simpson s discovery of the anesthetic properties of chloroform helped revolutionize surgery and removed the fear of pain and trauma.*

Nitrous oxide, and to a lesser extent ether, are still important drugs,

although chloroform has since been replaced by safer alternatives. Nevertheless, chloroform did show what sort of chemical substances would be most likely to have anesthetic properties. Chemically, chloroform is known as an halogenated hydrocarbon, and the medical literature contains examples of other substances in this category that were used as anesthetics but subsequently discarded as being too toxic.[32] Currently it is halothane, another halogenated hydrocarbon, that is widely used for major surgery.

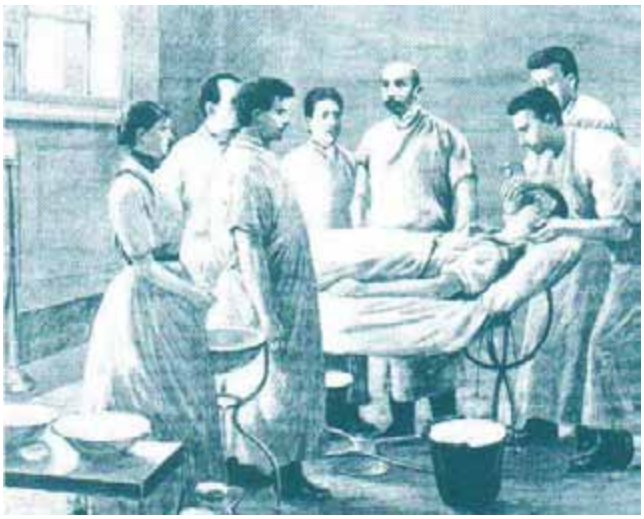
The first *local* anesthetic was cocaine, and its use for such a purpose was first suggested by Sigmund Freud.[6] Cocaine, a derivative of the coca leaf, had been used for pleasure as well as for medical purposes for centuries in South America, and by the 1870s several doctors had testified to its benefits in a wide variety of conditions. Then, in 1883, Freud commenced his own research, carefully experimenting on himself. He noticed that cocaine numbed the tongue and cheeks, and while others had described the same lack of sensation in the past, none had had the ingenuity to apply it to surgery.

Freud described cocaine's numbing effects to an ophthalmologist friend, Dr Carl Koller, who had been searching for an anesthetic for eye surgery. Strangely, in view of cocaine's long history of use, Koller carried out preliminary experiments on animals before doing the same tests on himself and an assistant. A solution of cocaine was applied to the eye, which was then assessed for sensitivity. The tests were repeated on other colleagues and on patients. They worked: cocaine could be used as a painkiller for people with eye conditions and as a local anesthetic for eye surgery.

Today, the most widely used local anesthetic is lignocaine, which resulted from a chemist's habit of tasting all the compounds he produced.[21] In 1935, Holger Erdtman at the University of Stockholm synthesized a chemical called isogramine. As was his practice, Erdtman tasted a trace of the substance and discovered that his tongue went numb! Using isogramine and another similar "tongue

numbing" chemical as their starting point, Erdtman and his research student synthesized a further 57 closely related analogues to find the most effective. Bergt Lundqvist, a colleague, tested compound LL30 on himself and suggested its full evaluation at the Karolinski Institute. LL30 turned out to be lignocaine, subsequently marketed by Astra in 1948.

A major advance in anesthesia during the 20th century was the development of curare as a muscle relaxing agent. For many operations it is advantageous for the muscles to be sufficiently relaxed so they can be easily separated for surgeons to work in the gaps between them.



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► *Surgical technique advanced rapidly once hygienic principles and anesthesia had been firmly established - the one removed the ever-present spectre of infection while the other gave the surgeon more time to work.*

Although this can be achieved with general anesthetics, high doses are required, with all their attendant hazards. The profound muscle relaxation provided by curare removed for all time the need for deep anesthesia and led to a dramatic decrease in the number of pneumonias and other complications following surgery. Once again, self-experimentation played a part[6] in defining the actions of purified curare but not before clinical studies had proved its value during operations.[21]

The idea to use curare originated from Lewis Wright, a medical consultant to Squibb, who noted that the Nebraska State Mental Hospital employed the drug to facilitate pelvic examinations in disturbed patients. Experiments

in which animals were dosed with ether and curare ended in disaster with all of the cats dying and the dogs becoming deeply distressed. Although the animal tests were abandoned, Wright pursued his idea and eventually persuaded Harold Griffith, an anesthetist at the Homoeopathic Hospital in Montreal, to try the drug on patients anesthetized with cyclopropane. Fortunately, Griffith's wide experience with cyclopropane convinced him that patients should also be kept on artificial respiration and so he unwittingly overcame the main problem with curare - that it paralyzes the respiratory muscles and therefore necessitates artificial respiration. The outcome of tests with a 20-year-old undergoing an appendectomy were so encouraging that Griffith went on to inject curare into a further 25 patients undergoing anesthesia. Within 18 months, this and other clinical trials confirmed the revolutionary role of the drug in making operations safer.[21]

**Advance of Surgery Without Animal Experiments**

With the discovery of anesthetics and the rebirth of hygienic principles (another success for clinical medicine[33,34]), the range of operations expanded rapidly as surgeons were able to take more time over their work. During this innovative period, many argued that surgical advances must come from clinical practice rather than animal experiments.[35] In 1882 the great English abdominal surgeon Lawson Tait, who has been called the father of surgical asepsis,[36] wrote that vivisection had done more harm than good in surgery[37] while Royal surgeon Sir Frederick Treves warned that after experiments on the canine bowel he was "much hampered" and had "everything to unlearn" when he came to deal with the human intestine.[38]

*▼Sir Frederick Treves argued that experiments on the canine bowel "much hampered" his work. "I had everything to unlearn," he wrote, "my experiments had done little but unfit me to deal with the human intestine."*

In 1930, Sir Berkeley Moynihan, president of the Royal College of Surgeons, spoke out against animal experiments during a speech at the Banting Research Institute in Toronto:[39]

***"Has not the contribution of the laboratory to the surgery of the stomach, for example, been almost negligible when it has not been potentially dangerous because divergent from human experience and therefore inapplicable."***

To some extent, the surgeons' fears had been incorporated into British legislation controlling animal experiments. The 1876 Cruelty to Animals Act forbade the use of animals to practice surgical skills and for the next 110 years[49] British surgeons learned their craft in the only sensible way, by work with human bodies in the mortuary, then by observation of senior surgeons during actual operations, and finally by taking over under the close supervision of experienced colleagues. Most significantly, this is reinforced by Dr J. Markowitz, author *of Experimental Surgery* (1954), who wrote:

***"the operative technique described in these pages is suitable for animals, usually dogs. However, it does not follow that it is equally and always suited to human beings. We refuse to allow the student the pretense that what he is doing is operating on a patient for the cure of an ailment."***

Nevertheless, the Cruelty to Animals Act did give surgeons the option to use animals to develop new techniques.

The opinions of surgeons who rejected animal experiments for the development of new operations cannot be dismissed today as irrelevant. The crucial issue is the underlying physiological and anatomical differences which make animal experiments hazardous. This is reflected in the almost universal failure of the first *human* transplant operations, despite extensive animal research.[33] Only after considerable clinical experience did techniques improve and survival rates increase. At Stanford University, for instance, 400 heart transplant operations had been carried out on dogs, yet as cardiac surgeon



▲ **A *Wartime operations:*** *Historically, the battlefield has proved invaluable in developing new surgical techniques. According to the Wellcome Museum of the History of Medicine, surgery for wounds of the chest and heart became a relatively common procedure during World War II with the result that many of the fundamental skills of heart surgery were developed.*

Dr Albert Iben pointed out, the first human patients died because of complications that had not arisen during preliminary experiments.[40]

### Clinical versus Basic Research

Although it may seem obvious that clinical research has the greatest potential to provide information about disease and its treatment, only one third of projects funded by the National Institutes of Health involve human subjects.[41] This is not altogether surprising because over the years scientists have greatly exaggerated the claims of "basic research", much of which involves animals, and effectively minimized the contribution of clinical investigation.

It is argued that although basic research may not have immediate clinical relevance, it is nevertheless necessary to provide the background knowledge for medical advances. But at the heart of the debate is competition over the allocation of research funds: if basic scientists can attribute most successes to laboratory work, they will naturally be at an advantage in their bid for resources. Not only that but

public opposition to animal experiments has persuaded some researchers to make the astonishing claim that most, if not all, medical advances have relied on animals!

▼ ***Dr M. Beddow Bayly:***
*"...fields of scientific research which have hitherto involved a vast amount of animal suffering will eventually be rendered humane as well as more truly scientific."*

The distortions became so great that the English physician Beddow Bayly decided to set out the vital role of clinical investigation in his book *Clinical Medical Discoveries* (1961). Bayly wrote: "The paramount need for a clear and documented account of past achievements arises from the prevalent custom of those medical authorities who set out to support and defend the practice of experimenting on living animals so far to distort historical facts as to create the impression in the mind of the public that every single medical diagnosis and treatment had depended for its discovery and application on vivisection .... Happily, even the briefest perusal of the available evidence shows the falsity of these claims and provides historical proof of the supreme value of clinical observation and experiment when contrasted with the doubtful and often misleading practice of animal experimentation."

In 1977, Comroe and Dripps carried out a survey of major advances in heart and lung research between 1945 and 1975 which purported to show that basic laboratory research had been especially critical to progress.[42] Yet Beeson notes[4] that "Our understanding of cardiac function and cardiac failure has been advanced more by clinical investigators than by physiologists during the past 50 years." Furthermore, Comroe's study was later criticized[43] as being "unscientific": Richard Smith, assistant editor of the *British Medical Journal,* noted that the choice of top advances omitted entirely the evidence that smoking was the cause of much cardiovascular and pulmonary disease even though he regarded it as "the most important therapeutic maneuver for most doctors treating lung and heart diseases." The evidence for the harmful effects of smoking derived not from basic laboratory research but from epidemiological studies of human beings.[44]

Physiologist Comroe had earlier criticized the first heart transplant surgeons for failing to explain to the public that the procedure had only been made possible through basic laboratory research.[45] These views were contradicted by the immunologist Robert Good, who explained that the key steps in developing heart transplantation, such as control of infection, development of anesthesiology, control of the immune system and more, were in fact triumphs of clinical investigation.[34]

Eleven years after Comroe and Dripps' claims were published, Dr Samuel Thier, then president of the Institute of Medicine, concluded that the balance of medical research in the United States was under threat because the importance of basic research was being overemphasized.[46] He explained how medical science is saddled with the myth that developments in clinical practice come from basic science. "The truth", he said, "is that the emperor has no clothes," innovations in clinical practice often coming first. For instance, Edward Jenner's discovery of vaccination against smallpox relied purely on clinical research[33] and preceded the basic sciences of virology and immunology by many years. Dr Thier also criticized the emphasis that had been placed on basic research into AIDS as opposed to public health research.

It is also disturbing that of the estimated 20,000 American physicians who are clinical investigators, about 5% discontinue their research careers every year.[47] Reasons commonly cited include difficulty obtaining funds and clinical responsibilities that do not permit sufficient time for research. More specifically, fewer young physicians are entering careers in clinical cancer research where the consensus is that grant proposals for work with human subjects are at a competitive *disadvantage* compared with those for laboratory research.[48] The problem is that scientists who review grant applications are frequently from disciplines other than clinical research. Nevertheless, even when reviewed by appropriate peers, clinical research applications fare badly compared with those for laboratory experiments.



▲ *Sight deprivation experiments have been carried out in laboratories worldwide and are often justified by claims that they have contributed to the treatment of amblyopia (lazy eye). Yet critics argue that it is really human clinical studies that have been responsible for almost every advance.*[50]

While there will always be intense competition for research funds, policy makers may care to reflect on the preposterous situation where more is allocated to research with animals than to investigations of our own species! The equivalent would be for veterinary scientists to spend more on human clinical observations than on research into animal diseases, clearly an unthinkable proposition.

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