Section of the History of Medicine

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President's Address

Three Early Masters of Experimental Medicine – Erasistratus, Galen and Leonardo da Vinci

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It commonly happens that realities exist in the history of human affairs long before they acquire the dignity of a name. This is true of experimental medicine. Since the concept of experiment came into general acceptance only after the sixteenth century the word did not appear in our vocabulary until that time, and it has become customary to refer the origins of experimental medicine to that era. It has, indeed become so much an accepted practice to deny the ancient Greeks and men of the Renaissance the experimental approach that I feel it is time that this attitude should be reviewed and readjusted.

How do we define the term 'experimental medicine'? I know of no better definition than that of Claude Bernard (1957), who called it 'induced observation'. Comparing the methods of observation and experiment Bernard said: 'With observation and experiment a fact is simply noted; the only difference is this – as the fact which an experimenter must verify does not present itself to him naturally he must make it appear, i.e. induce it for a special reason and for a special object.' Thus an experiment always involves a preconceived idea, a technique of planned procedure, and a comparison, which we nowadays call a control. If the preconceived idea is vague the experiment consists in essence of merely looking to see. As Bernard says: 'Groping experiments which are very common in physiology and therapeutics . . . may be called *experiments to see*.' Lest we should underrate this kind of approach it is to be noted that it was from just such an 'experiment to see' that Bernard himself made the discovery of the mode of action of curare. But, as Bernard stresses, this kind of experiment should be done only as a means of acquiring more precise preconceived ideas upon which to base more intelligent experiments.

It is most often in the skilful design and technical performance of the induced observation or experiment that the mastery of the experimenter is revealed. This is the part of the process which is most personal though its results, with their interpretation, must be most impersonal. And here lies the gap between the tidy-minded theorists of Baconian inductive logic and the often untidy artists of creative science, whose unique work is to provide those firm observations upon which inductive thought can be based. Men with the power of such achievement I call masters of experimental medicine; and it is for this capacity I propose briefly to review the work of Erasistratus, Galen, and Leonardo da Vinci.

The commonest and the most fruitful of the preconceived ideas applied to experiment in medicine are those derived from the basic sciences of the day. Of chemistry there existed none in the days of the three men we are considering. But an elementary form of physics founded on the principle of the *horror vacui* extended far back even into pre-Hippocratic times. Indeed this principle was used by the Hippocratic writer of the work, Ancient Medicine, when he asks: 'Which structure is best adapted to draw and attract to itself fluid from another body, the hollow with the wide opening, the solid and round, or the hollow and tapering?' (Adams 1849) and he answers the question through the analogy of cupping, concluding that it is the bladder, the head, and the womb, which are hollow organs with a long narrow entrance.

Strato

Intensive experimental analysis of the phenomena of the *horror vacui* was carried out by the man who was Head of the Lyceum at Athens, after Aristotle and Theophrastus about 300 B.C. This man, Strato of Lampsacus, has suffered eclipse through the complete loss of his works. It was only in 1893 that Hermann Diels unearthed a fragment of his work from which we can gain some idea of Strato's experiments on hollow vessels; from this I shall quote. First demonstrating that empty vessels containing air cannot be filled with water, Strato went on to show that the particles of air in a vessel can be compressed by positive pressure and thinned by negative pressure. Strato stated it thus: 'Vessels which are generally believed to be empty are not really empty but are full of air. Now air consists of minute particles of matter for the most part invisible to us. Accordingly if one pours water into an apparently empty vessel a volume of air comes out equal to the volume of water poured in. To prove this make the following experiment. Take a seemingly empty vessel, Turn it upside down, and plunge it into a dish of water. Even if you depress it until it is completely covered no water will enter. This proves that air is a material thing... now bore a hole in the bottom of the vessel. The water will then enter at the mouth while the air escapes by the hole' (Farrington 1953). So far the experiment is almost a repetition of one described by Empedocles in 450 B.C., but Strato further develops his experiments. 'If', he says, 'the particles of air are separated from one another, with the creation of larger empty spaces between them than is natural, then their tendency is to draw together. Take a light vessel with a narrow mouth, suck out the air, and take your hands away. The vessel will remain suspended from your lips because the void will tend to pull the flesh in...' Strato then goes on to show that vacua exist in nature in very small scattered form, by taking a large metal sphere into which a narrow copper pipe was inserted. 'One who puts his lips to the pipe can blow a great quantity of air into the sphere without any of the contained air escaping. This constitutes clear proof that the particles of air in the sphere are compressed into the vacua between the particles.' 'If the reverse experiment be tried, a great quantity of air in the sphere can be sucked out without any other air getting in. This experiment conclusively demonstrates that the formation of a continuous vacuum takes place in the sphere. Summing up we may say that all bodies consist of tiny particles of material between which are interspersed vacuums smaller than its parts... it is only in so far as one of these substances departs that another can enter to occupy the empty space.'

The childish simplicity of these experiments may make us smile, but this must not be allowed to obscure for us their importance. The 'tiny particles' and the vacuums were for the advanced thinkers of 300 B.C. what the muons and pions are for our own time.

Erasistratus

I have cited these experiments of Strato since he was living in Alexandria at the same time as his younger contemporary Erasistratus upon whom he exerted a great influence both with regard to the results of his experiments on air and the nature of his experimental method. Erasistratus was first an anatomist whose descriptions of the heart and brain evince a knowledge of detail that was not reached again until the days of Vesalius. But his greater contribution was towards experimental physiology and pathology. Unfortunately, as with Strato, all his works have been lost; they were probably destroyed when the great library of Alexandria was burnt down. We have our accounts of his work therefore only through the scrappy references to him in the works of his successors, chiefly Galen, and Galen was stimulated to bitter criticism of Erasistratus for the purely mechanical nature of his predecessors' physiological theories. But Galen tells us enough to make it evident that Erasistratus performed innumerable experiments on animals which were designed to apply Strato's science of pneumatics to human physiology and pathology. It was for example, on this pneumatic basis that Erasistratus conceived of air being drawn into the lungs by the negative pressure within the thorax on inspiration. This sound explanation he unfortunately pushed too far. He thought that similar negative pressure extended into the heart in diastole, air thus being drawn through the pulmonary veins into the left ventricle. Moreover, assuming that arterial diastole was an active movement, he found the arteries to be full of air so attracted from the left ventricle into their lumens. Thus he reached the conclusion that in health the arteries contain air, not blood. Flesh Erasistratus considered to be composed of the terminal interwoven network of arteries, veins and nerves, and thus he came to interpret muscle tone and action as derived from the tension of air within the small arterioles. Blood he considered to be conveyed in the veins and right ventricle alone; only in disease did it leak over through peripheral anastomoses into the arteries, where it gave rise to the heat, swelling and pain of inflammation. The movements of all the body fluids Erasistratus found by his experiments to be due to pressure differences. In the stomach digestion was achieved by heat and mechanical pressure; nourishment reached the liver by being squeezed along the portal vessels; bile was formed in the liver by filtration from the blood; urine was formed by filtration through the kidneys. In all his physiological theories Erasistratus persistently ignores the humours, apparently never even discussing them. Herein lies the cause of Galen's frequent and bitter references to his work.

Few indeed are the instances where we have the opportunity of hearing Erasistratus speak for himself, but we do have a brief comment he made on the subject of research. 'Those', he says, 'who are altogether unaccustomed to research are, at the first exercise of their intelligence befogged and blinded, and quickly desist owing to fatigue and failure of intellectual power, like those without training who attempt a race. But one who is accustomed to investigation, worming his way through, and turning in all directions, does not give up the search his whole life long. He will not rest but will turn his attention to one thing after another which he considers relevant to the subject under investigation, until he reaches the solution to his problem' (Farrington 1953).

Two examples must suffice to illustrate the experimental genius of Erasistratus; one shows his enthusiasm, and one his skill. Celsus tells how Erasistratus, with his colleague Herophilus, opened men whilst these were still breathing, and 'observed parts which beforehand Nature had concealed, their position, colour, shape . . . For when pain occurs internally, neither is it possible for one to learn what hurts the patient unless he has acquainted himself with the position of each organ or intestine; nor can a diseased portion of the body be treated by one who does not know what that portion is like'. Here Erasistratus' experimental zeal has brought him condemnation on ethical grounds throughout the ages. Even that enthusiastic advocate of vivisection, Claude Bernard, condemns him. But it does clearly reveal to us the experimental nature of Erasistratus' attack on problems of physiology and pathology.

His skill is better illustrated by his attempt to show that evaporation of invisible particles from the body continuously takes place. It is described by the writer of the manuscript called Anonymus Londinensis, thus: 'If one were to take a creature, such as a bird . . . and were to place it in a pot for some time without giving it any food, and then weigh it with the excrement that visibly has been passed, he will find that there has been a great loss of weight, plainly because, perceptible only to the reason, a copious emanation has taken place' (Jones 1947). This loss of weight Erasistratus claimed was replaced by nutriment and breath. Thus he anticipated the quantitative weighing experiments of Sanctorius in the seventeenth century, nearly 2,000 years later.

Galen

One measure of the greatness of Erasistratus as an experimenter consists of the innumerable experiments undertaken 400 years later by Galen to refute his results. Indeed it is in this mission that Galen often reveals his own experimental genius, an aspect of his work which has for too long been swallowed up by the dark complexities of Galen the dogmatist, the view of him which has become traditional.

Galen in fact gave a great deal of attention to methods of acquiring medical knowledge. His first work, written when he was 20 years old was entitled 'Medical Experience'. It was devoted to a study of the methods of the dogmatists and empiricists, and sanely concludes that the best method in medicine combines something of both. Experiment Galen specifically includes as a mode of medical experience and he is under no illusion regarding the origins of some of the preconceived ideas of the experimenter. In his work 'On the Medical Sects' he writes: 'What is called improvised experience is when one deliberately tests something that has been suggested by dreams or the like. Further there is another kind of experience, the imitative; in this something which, occurring either by nature, chance, or improvisation, has proved helpful or the reverse, is tested anew in the same diseases by Experiment. . . . Having imitated, not once, nor twice, but repeatedly, the treatment which proved salutary on a former occasion, and having found it has the same action . . . they give a fact like this the name theorem, deeming it now worthy to form an integral part of the medical art.' Such a collection of theorems Galen states is known as Medicine. These theories are built up, he affirms, largely by analogies. Every transition of this kind, i.e. by analogy, he describes 'as a road to discovery, but', he adds, 'Experiment is needed before it actually becomes a discovery'.

It will be seen that Galen approaches Francis Bacon in his comprehension of the gradual inductive method. Unlike Bacon, however, Galen *could* perform experiments as well as think about them. His knowledge of anatomy from personal dissection of animals was vast; man was the animal of which he had least direct knowledge. He reports dissection, or vivisection, of pigs, goats, sheep, apes, horses, asses, mules, cows, lynxes, stags, bears, weasels, mice, serpents, fish, birds, and at least one elephant; modestly confessing that he had not dissected ants, gnats or fleas. It is a range which vies with that of Harvey.

As an anatomist Galen revealed structures whose function he wished to test. To this he was particularly stimulated by the work of his predecessor Erasistratus. His method was for the most part simple. Almost all his experiments in physiology were based on the principle of ablation; he cut nerves and muscles; he tied tubes; and observed the results.

Experimental brilliance does not necessarily coincide with important results. It is indeed in one of his least momentous experiments that he best displays his experimental mastery. Asclepiades, his predecessor as a famous physician in Rome, had asserted that the excretion of urine was directly into the bladder from the blood. Galen set out to demonstrate that this was the function of the kidneys. He describes his procedure thus in his work 'On the Natural Faculties':

'Now the method of demonstration is as follows. One must divide the peritoneum in front of the ureters; then secure these with ligatures; and next, having bandaged up the animal, let him go (for he will not continue to urinate). After this one loosens the external bandages and shows the bladder empty, and the ureters quite full and distended – in fact almost to the point of rupturing. On removing the ligatures from them one plainly sees the bladder becoming filled with urine. Then, before the animal urinates one has to tie a ligature around its penis, and then squeeze the bladder. Nothing goes back through the ureters to the kidney . . . One now loosens the ligature from the animal's penis and allows him to urinate. Then one ligates one of the ureters and leaves the other to discharge into the bladder. Allowing some time to elapse one now demonstrates that the ureter which was ligated is obviously full and distended, whilst the other, that from which the ligature has been taken, is itself flaccid, but has filled the bladder with urine. Then again one must divide the full ureter, and demonstrate how the urine spurts out of it, like blood in the operation of venesection; after this one cuts through the other ureter also, and both being thus divided one bandages up the animal externally. Then, when enough time seems to have elapsed, one takes off the bandages; the bladder will now be found to be empty, and the whole region between the intestines and the peritoneum full of urine, as if the animal were suffering from dropsy. If anyone will test this for himself on an animal I think he will strongly condemn the rashness of Asclepiades.'

The more closely one examines this series of experiments the more one must admire their beautiful design, and the careful use of control observations at each stage, let alone their superb technical skill in animal experiment. It is still being written by modern historians that the ancients never understood the principle of control experiments; surely it is quite clear from this example, Galen did.

The exhibition of such experimental skill on a problem involving the flow of fluid between viscera leads one to enquire how Galen fared when he directed his attention to the flow of blood into and out of the heart, for he worked hard on this problem experimentally. The exposure of the beating heart and lungs in living sheep and pigs he found to be of great technical difficulty, death of the animal from pneumothorax being only too common. He did however eventually achieve this, and after describing his methods in meticulous detail, and with evident pride, Galen says in 'On Anatomical Procedures': 'When the heart is exposed, your task is to preserve all its functions unimpaired, as in fact they are, so that you can see the animal breathing and uttering cries and, if loosed from its bonds, running as before . . . And what is strange in that? The slave of Maryllus, the mime-writer, whose heart was once exposed, was cured and still lives . . . ' and Galen goes on to describe the case of this slave who had a chronic osteomyelitis of the sternum, in whom he successfully removed the affected bone, so exposing the heart, without producing a pneumothorax.

With the heart of the animal exposed by removing the sternum, Galen examined it for the relation of its systole and diastole with the movements of the main blood vessels. But he could no more analyse this in the quick-moving heart of the pig than Harvey could 1,500 years later. Galen tries to elucidate the problem by tying the pulmonary vein, but at each attempt he produces a pneumothorax. 'It is not possible to ligature the course of the vessel [pulmonary vein]' he laments. 'It can be done round the base of the heart, but the animal dies at once.' He is baulked; he has reached the limit of his technical skill and so he failed to break Erasistratus's idea of active cardiac diastole. How could he have overcome this obstacle? We know from his experience of comparative anatomy that he had dissected serpents. Here was the way, but he did not think of it. It was not until Harvey selected snakes for vivisection because of the slow action of their hearts that systole and diastole of the heart and main vessels were successfully analysed. This is a momentous example of the importance in experimental medicine of choosing the right animal.

But Galen did establish, by an experiment which Harvey repeated, that, contrary to Erasistratus, the arteries contained blood in life. This meant communication between veins and arteries. Ignoring the peripheral anastomoses between veins and arteries which Erasistratus had postulated he sought for some other communication between them, and found it in the 'invisible pores' which he suggested communicated between the right and left ventricles through the septum of the heart, whereby in diastole blood was sucked from the venous into the arterial tree. It was a logical but unhappy hypothesis the consequences of which need no elaboration.

The most momentous of Galen's experiments were those he performed on the spinal cord and nerves. Many of these were prompted by a desire to analyse the movement of respiration and phonation. These experiments on pigs he summarizes as

Fig 1 *Galen's public demonstration of division of the recurrent laryngeal nerve in the pig. From the Froben Edition of Galen's Works, 1586*

follows: 'If you sever [the spinal cord] completely between the 3rd and 4th cervical vertebræ, the animal at once ceases to breathe. Not only does the thorax become motionless, but also the whole body below the section. If [section is made below] the 6th cervical vertebra, all the muscles of the thorax become motionless immediately and the animal breathes in only by the diaphragm. Transverse sections below this vertebra permit other parts of the thorax to move . . . The further you advance towards the lower vertebræ the more muscles of the thorax will you leave active. However this does not happen to the pair of nerves entering the phrenes [diaphragm]; when all the other nerves are destroyed the animal breathes with diaphragm alone. When the spinal marrow is cut in the middle, straight downward, it does not paralyse either [set] of the intercostal muscles, or those in the loins or legs. When cut transversely, if only the half is severed, all the nerves on that side are paralysed in series.' Not until Brown-Séquard and others repeated these experiments in the middle of the nineteenth century, were Galen's brilliant observations repeated and appreciated.

In the course of his neurological experiments Galen had the good fortune to cut the recurrent laryngeal nerve of a squealing pig; the sudden silence of the consequent aphonia was too dramatic to be missed. This discovery of the innervation of the vocal cords gave him one of his proudest moments. His friends hired a special hall for him to demonstrate the experiment before the foremost philosophers of Rome. One can almost hear Galen saying to them; 'I want you to realize that what I am describing was discovered by me, that no anatomist knew a single one of these particulars and hence made many errors in connexion with the larynx' (Walsh 1926). This moment, illustrated in the Frohen Edition of Galen's works in 1586, shows convincingly how fashionable physiological experiment had become in the Rome of Galen's day (Fig 1).

Dissatisfied with the purely physical explanations of physiology advanced by Erasistratus, Galen developed the theory of the humours to be found in some of the Hippocratic works. In these humours, and in his postulates of what he called 'natural faculties' such as attraction, adhesion, alteration and assimilation, it is possible to see him reaching out to a kind of hypothetical chemistry. Many of his experiments, undertaken to demonstrate these forces were ingenious, but necessarily erroneous. To take one example, from his investigations of the act of swallowing: ingeniously he demonstrates that after either transverse or vertical incisions through the coats of the œsophagus swallowing can still take place. From this in 'On the Natural Faculties' he deduces that, 'the stomach draws food to itself by means of the gullet as though by a hand. Just as we ourselves in our eagerness to grasp something stretch out our whole bodies along with our hands, so also the stomach stretches itself forward along the gullet, which is, as it were, a hand'. In such experiments, to demonstrate the faculty of 'attraction', Galen only too clearly illustrates the dangers of the experimental method in the service of a premature general theory. Such a use of experiment helped to consolidate that massive body of Galenic dogma which was found so impregnable by his successors through the centuries.

Leonardo da Vinci

For some mysterious reason the fashion for experiment amongst the intelligentsia of Rome died with Galen. And until the Renaissance the quest for experimental knowledge, apart from isolated examples from men like Roger Bacon, seems to have been quenched by the Christian and Moslem faiths. One of the first to break through this barrier into experiment was Leonardo da Vinci, whose methods, like so many of his other activities, were unique. There are three main reasons for this; first, his approach to experiment on animals was primarily that of the artist; secondly, Leonardo was an anti-vivisectionist; and thirdly his language of record was dominantly visual.

Of the artistic approach to anatomy and physiology at this time one need say no more than that it supplied the impulse to fresh observation which was not forthcoming from the medical profession. This Leonardo shared with his contemporary artistic colleagues. His anti-vivisectionist views are however less well recognized. His deep repugnance to killing animals is expressed in the words: 'Our life is made by the death of others. Man and animals are sepulchres . . . making life out of the death of the other; taking pleasure in the misery of others, and making themselves the covering of corruption' (Richter 1955). These sentiments led him to be a vegetarian in his diet, and to abjure vivisection in his experiments. Apart from the pithing of a frog, not one of his experiments in physiology was performed on living animals. An apparent exception, the well-known observations of the movements of the knife or 'spillo' in the hearts of dying pigs, were made by him as he watched the routine slaughtering of these animals in the abattoir. Vivisection is considered by most physiologists as the *sine qua non* of experiment. How then did Leonardo approach his biological experiments?

Leonardo nowhere discusses his methods as such, and one has to construct his approach to experiment from the disorder of his notes. Here he repeatedly insists on the necessity of personal observation, on the necessity of mathematics, by which he means geometry, and on the application of the laws of physics, particularly mechanics. 'Mechanics', he writes, 'is the paradise of the mathematical sciences because by means of it one comes to the fruits of mathematics' (Keele 1952). It was through his deep comprehension of the geometry of forces that he was able to make those conversions and transmissions of power which crystallized out in his many inventions of machines, such as water-mills, printing presses and lathes. It was through his understanding of the geometry of forces that he anticipated the principle of inertia, so that it was commonly named after him until Galileo and Newton stated it in clearer mathematical form. The same holds for his conception of the force of gravity and the parallelogram of forces. It was through his geometrical vision that he could see that: 'Just as a stone thrown into the water becomes the centre and cause of various circles, and the sound made in the air spreads in circles, so any body placed within the luminous air spreads itself out in circles and fills the surrounding parts with an infinite number of images' (Richter 1955). Each of these statements is verified by many painstaking experiments. Thus it was he reached a conception of the wave-motion of light and sound.

But of all media water was his favourite, for this gave him the clearest visual evidence of the dynamic geometry of active forces; and water was his main professional pre-occupation as an engineer in charge of the maintenance of the waterways of Lombardy. In the Martesana and Ticinello canals he could see the formation of vortices, draw their shapes, and construct models for experiment on their variations.

When he came to the study of the human body he brought with him this mass of experimentally acquired knowledge shaped into mechanical principles. For Leonardo the movements of the muscles and bones were opportunities for application of the laws of the lever, and the movement of the blood was an exercise in hydrodynamics. Discussing how to present his anatomical studies he writes: 'Arrange it so that the book of the elements of mechanics, with examples, shall precede the demonstration of the movement and force of man.... By means of these you will be able to prove all your propositions' (Keele 1952). His approach was thus much more akin to that of Erasistratus than Galen. Indeed chemistry existed for Leonardo no more than it did for Erasistratus or Galen; the alchemy of his day Leonardo despised and abjured.

Thus one may look upon Leonardo's anatomical studies as the preliminary investigation of an apparatus capable of exerting forces as a machine. Throughout them all one can see his pre-occupation with the mechanical significance of what he dissects. Having obtained the essential knowledge of the mechanical principles of the dissected part, he takes it outside the body by creating his imitation of it in the form of a model. Here he finds freedom in studying and controlling variables necessary to reach their underlying principles of action. He applied this method, for example, to the study of the eye in relation to light (Fig 2), making models of the cornea and lens, and placing his own eye in the position of the optic nerve, where he considered the sensitive part of the retina should lie. It was during these experiments that he discovered the camera obscura, which was constructed merely incidentally as part of his model of the human eye.

Thus Leonardo's technical experimental skill was *not* that of the vivisectionist; it was that of the sculptor and engineer. His experiments represented for him reproductions of the powers of Nature in the same way as his finest paintings were created as symbols of Nature and her Laws.

Leonardo's methods of recording his experiments were more unusual even than his methods of making them. He was very much aware of the

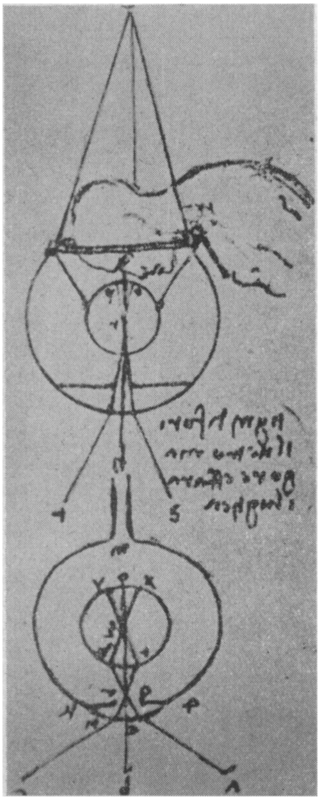

Fig 2 *Leonardo's construction of a model eye. His own eye is placed at the position of the optic nerve, as depicted in the figure alongside. The large glass globe, filled with water, has the solid glass lens suspended within it. The whole is made to be suspended so that the head of the observer can be fitted into it. (MS D 3v, Institut de France, Paris)*

insufficiencies of word-language. Languages, he asserts, have many words for the same thing; they vary from century to century, from one country to another; languages are liable to pass into oblivion, and they are mortal like all created things. In contrast he repeatedly affirms the advantages of visual images for conveying scientific information. Only in this way, he asserts, can one speak a direct, universal and permanent language which circumvents errors of translation and verbal misunderstanding. It is for this reason that whole pages of his manuscripts are often found full of drawings only, with no explanatory words. Often his thought is to be found in isolated diagrammatic sequences. When he does use words he is often repetitious, striving to reach his meaning by writing passages not once but two or three times. This he does more often towards the end of his life, particularly in his work on the heart. This choice of visual images as language serves to make Leonardo comprehensible to-day in unique fashion; but it also limited his formulation of abstract laws, reducing him to the description of details and particulars. As a result his scientific achievement has been severely criticized on the grounds of his lack of great generalizations.

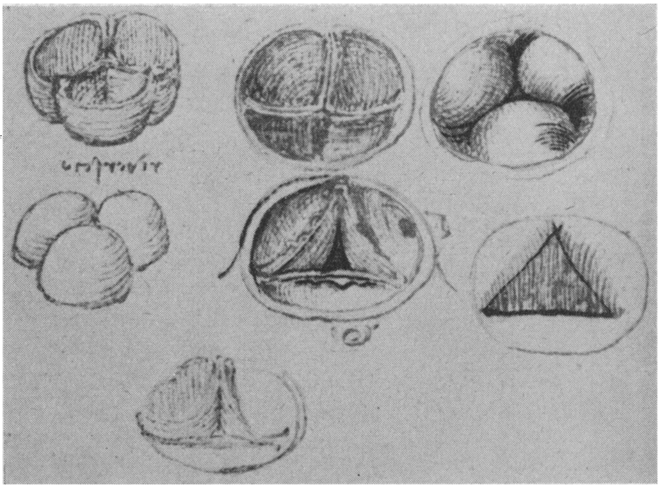

Fig 3 *Aortic valves, removed, and studied from above and below, open and shut. The orifices of the coronary arteries are clearly shown, and the triangular aperture of the opened valve cusps emphasized. (QA II 9v)*[1]

All these aspects of Leonardo's approach to experimental physiology are evident in his work on the heart. Of all organs of the body this fascinated him most, for its hæmodynamic problems offered a direct challenge to his experience gained from his work on the movement of water. For these reasons, and because a series of experiments which he made on the heart and aorta have some contemporary interest, I shall confine illustration of his methods to this work.

Early in his anatomical studies he satisfied himself that, contrary to Galen's opinion, the heart is a muscle pump, and that its movements of systole and diastole are governed by the same mechanical principles as other muscles. This led him to make intensive study of the heart valves, all of which received individual attention. The three leaves of the tricuspid valve, for example are drawn unrolled, as it were, in order to examine the part played by the cordæ tendinæ and papillary muscles in opening and closing the orifice. But the aortic valve received more intensive study than any. Its cusps were drawn *in situ*, open and closed, and removed from the body (Fig 3). The triangular shape of the open aortic orifice was repeatedly noted, and the dilatation at the root of the aorta, named after Valsalva, was carefully drawn.

[1] QA = Quaderni d' Anatomia (Vangensten *et al.* 1911-16)

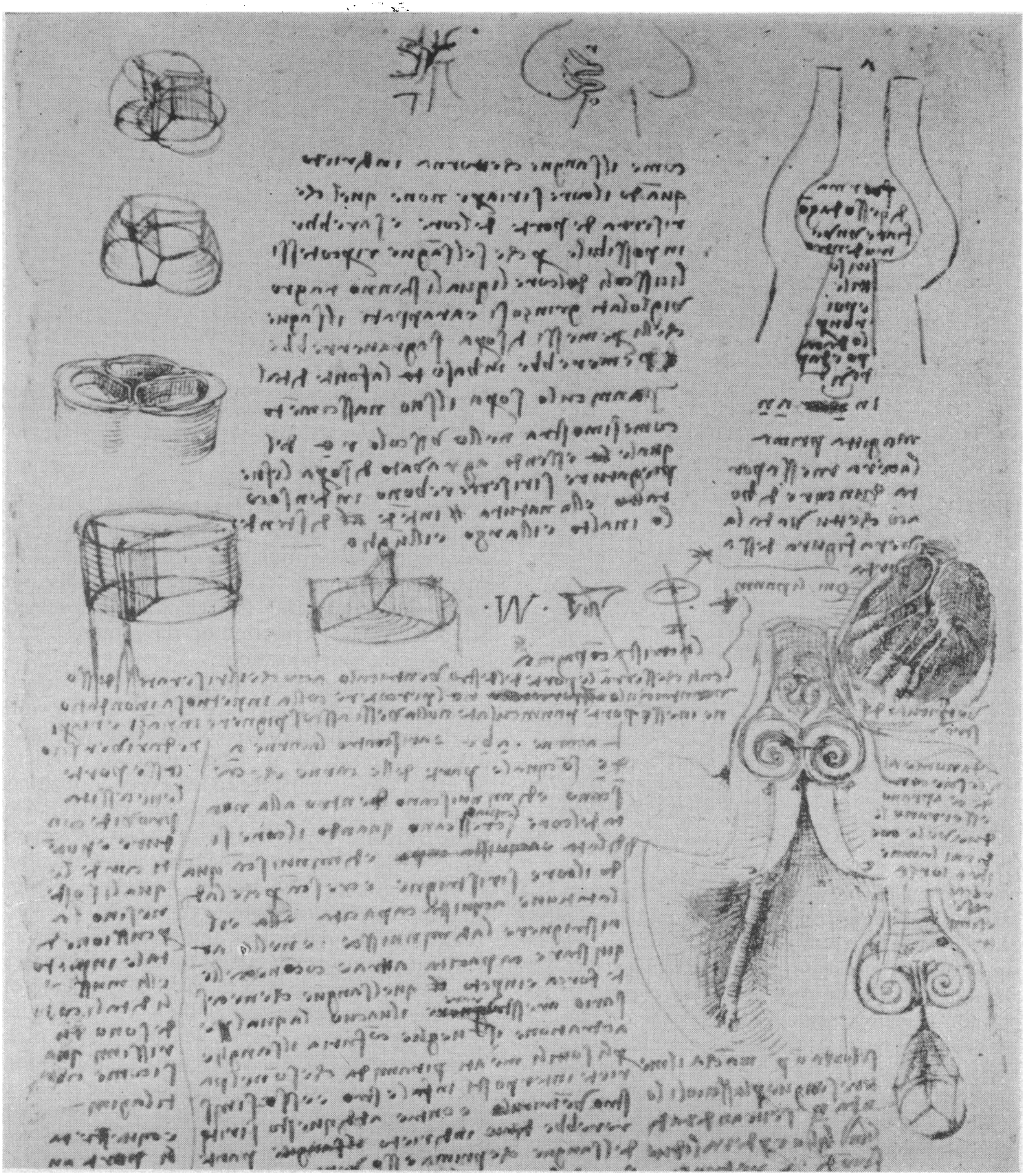

Fig 4 *The page of manuscript on which Leonardo gives constructional diagrams of an artificial aorta and valves. The scheme for making a cast of the aorta and valves is enclosed in the sketch (top right). The constructional diagrams extend to the left, and upwards on the left margin of the page. The written words make no comment on the diagrams. The remaining figures show the return stream of blood by which the aortic valves are closed. At the top of the page is drawn the buckling of the valve cusp which would occur if the blood pressed straight down on the cusp. (QA II 12 r)*

Having satisfied himself of the shapes and relations of this region of anatomy, Leonardo proceeded to his next stage of experimental investigation, that of creating a working model of the parts, in imitation of Nature. Now this is the very problem upon which so much work is being done to-day, when it has become possible to approach the aortic valves surgically. Leonardo's attempt to make an aortic prosthesis may thus be looked upon as an anticipation of what is being attempted to-day. It may be that present day workers could gain some useful information from his efforts.

First Leonardo made a cast of the base of the aorta, a task of great difficulty even for a man of his manual dexterity. He began by making a wax cast of the aorta; over this he made a hollow cast of gypsum. This he lined by a sheet of blown glass. He makes a special note that the wax must be poured right into the heart through the valve orifice, or 'gateway of the heart', as he calls it, 'to see its true form'. On this particular page of manuscript (QA II 12r) (Vangensten *et al.* 1911-16) there are several drawings of the stages of this construction of the aortic valves, of which he gives no verbal description at all (Fig 4). Because of this they have received no notice from commentators. But his procedure becomes clear if the drawings are read from right to left, which is Leonardo's usual sequence of diagrammatic thought, since he was left handed, and always wrote his words in this direction. Here can be seen his construction of a tripartite flange on a circular base which is then inserted into a tube. The vertical flanges are then cut off and pared down to the hollowed shape corresponding to three aortic cusps . . . but the clumsiness of word description compares badly with the clarity of Leonardo's drawings. This model of the valves was then incorporated in the glass mould of the root of the aorta, 'To see in the glass what the blood does in the heart when it shuts the opening of the valves' (Keele 1952).

On another page (QA IV 11v) (Fig 5) he illustrates his tripartite model divided longitudinally into its three separated parts. In this model he has exaggerated the sinuses of Valsalva, and widened the base into a shape which is shown fitted to the left ventricle of a bull's heart. He also shows by a series of constructional diagrams how the model is designed. His only verbal comment on them is the few words placed between the figures; 'Fa questa prova di vetro a movici dentro a cise panicholo' 'Make this glass trial (experiment) and move in it the pannicles (valves)' (Keele 1952, p 81).

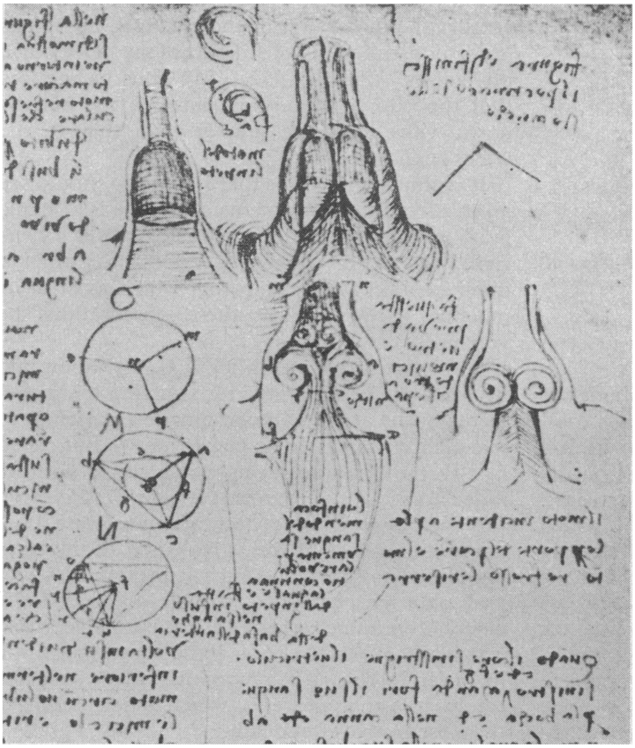

Fig 5 *Leonardo's model of the aorta and its valves, divided into three parts to show its mode of construction; the design is represented diagrammatically below in three circular figures. The closure of the aortic- valve cusps by the return eddies of blood is shown in the central figure. Beside this are the words 'fa questa prova di vetro e movici dentro a cise panicholo'. (Make this glass-trial and move in it the pannicles). (QA IV* 11*v*)

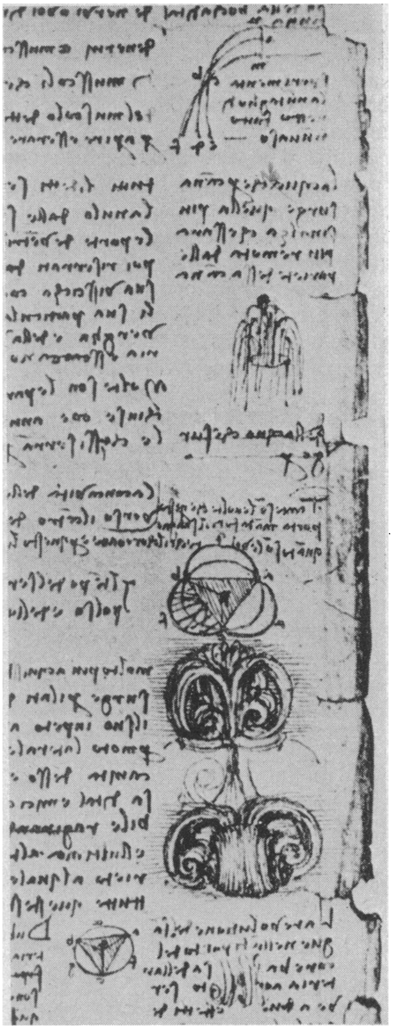

Fig 6 *Studies of the movement of fluid through pipes of different shapes. At the top, fluid emerging from round-ended pipes is drawn. Below, diagrams of the triangular aortic orifice are accompanied by sketches of the fluid trajectories passing through such an orifice.* (*QA IV* 11*r*)

So much for his construction of the model of the aorta. How did he propose to 'make his trial' with it? He uses the same methods that he has practised for so many years in his studies on the movements of water in rivers and streams. Amongst these are to be found several in which he makes model channels of glass, in which, in order to follow the fluid veins he notes: 'Let the water that strikes there have millet or fragments of papyrus mixed with it, so that one can see the course of the water better from their movements.' Elsewhere he suggests dropping in a few grains of panic grass, 'because by the movement of these grains you can quickly know the movement of the water that carries them with it' (Keele 1952, p. 80). Such were the methods he used to observe the movement of fluid through his model aortic valves.

He begins the observation of such movements with the simplest case, that of water emerging from a round-ended pipe (Fig 6). He then modifies this by making the pipe of triangular section with dilatations corresponding to the sinuses of Valsalva; and he finds that the fluid forms three vortices. This circular motion of the blood he considers responsible for the dilatations at the base of the aorta which Leonardo calls the 'hemicycles', and we the sinuses of Valsalva. Repeatedly Leonardo demonstrates that this returning circular motion of the blood closes the aortic valve cusps by a lateral not a vertical force, pushing them against one another like three bellying sails. This returning stream of blood, 'beats the valves with composite motion', he writes, 'raising and stretching them; and shuts them against the opposite valve cusps'. The valve cusps cannot be closed from above, he asserts, since this would buckle the cusp upon itself. He makes many drawings of this mode of closure of the aortic valve. He even goes so far as to consider the velocity of the blood in the various stages of its movement through the aortic valve. From his experiments on water he had discovered that the velocity of flow varies inversely with the diameter of the channel: 'the greater the velocity the smaller the dimension of the passage', he writes, 'as demonstrated in the 3rd part of my "Discourse on Waters" ' (Keele 1952, p 84). Thus he deduces that the rate of blood-flow through the narrow aortic valve must be greater than that in the wider hemicycles.

It is almost incredible that Leonardo should see all this from the movements of the seeds of panic grass in his glass models of the aorta. But if he is right, closure of the aortic valves has rather a different mechanism from that which most of us imagine. How far can these observations be verified?

Some years ago with Mr I K R McMillan and his remarkable apparatus for studying the movements of the aortic valves we made an attempt to see such currents as Leonardo drew. But, technically the apparatus was not suitable and we failed to see the movements of the fluid clearly. We did however note how accurate were Leonardo's drawings of the valve cusps in the open and closed positions. A comparison of the drawings and photographs from Mr McMillan's (1955) cinephotographic series (Fig 7) makes it clear that Leonardo must have seen these cusps in motion in order to draw their wrinkled edges so accurately; it is an appearance which is not present in the closed valve after death.

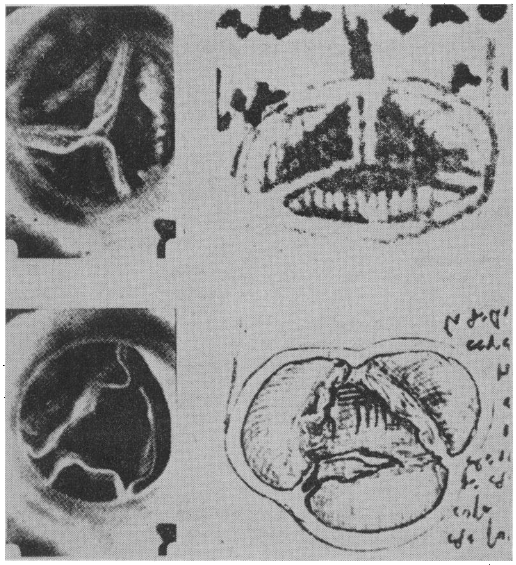

Fig 7 *The aortic valves open and closed. A comparison between the appearances as drawn by Leonardo and cinephotography. Note the dark triangular shadows in the closed cusps, and the wrinkled edges of the open cusps, in both representations.* (*QA IV* 12*r*)

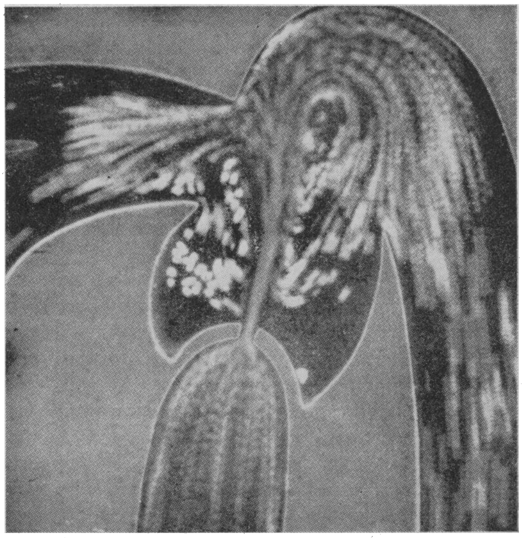

Fig 8 *X-ray studies of jet turbulence, using radio-opaque lucite pellets. Note the reflux component of the movement.* (*Reproduced by kind permission from Dotter & Frische, 1958*)

Another approach to the problem has been made by studies of velocity in the great vessels of human beings. Using a Petôt tube inserted into the pulmonary artery of human beings Jameson (1955) has found an increasing velocity of blood in early systole, followed, he writes, 'by a period of backward flow lasting over 0·1 sec and ending with the completion of the dicrotic notch. The duration and timing of the backward flow suggest that it is associated with retrograde movement and closure of the semilunar cusps'. This statement, made in 1958 comes very close to confirmation of Leonardo's conception.

Complete confirmation, however, can come only through actually seeing the blood flowing through the aortic valve; and this is not beyond the powers of present possibility. However, so far as I know, it has not yet been done. Radiological studies of the turbulence of fluid jets in models, which remind one forcibly of Leonardo's experiments, were made in 1958 by Dotter & Frische, using solid radio-opaque lucite pellets. Like Leonardo they found the movement of a particulate medium necessary to reveal fluid turbulence. One study is remarkable for showing such radio-opaque pellets flowing backwards from a jet of fluid in a manner very reminiscent of Leonardo's hemicycles (Fig 8). The next stage, of course, would be to demonstrate the corresponding turbulence in a human aorta. I am anxious to see this performed.

But the outcome of such verification is really irrelevant to my endeavour to illustrate Leonardo's worthiness to be considered, not only as a master of the visual arts and physical sciences, but of experimental medicine as well. This seems to me to be vindicated by this particular series of experiments. They are all the more astonishing when we realize that they were performed by a man who was ignorant of the circulation of the blood.

But my main motive has been to emphasize a fact which seems too little recognized; that experimental medicine was successfully inaugurated long before the days of Harvey. The three exponents whom we have so briefly considered made this achievement against the intellectual outlook of their times. They worked in a hostile zeitgeist, and therefore could expect no contemporary appreciation of their efforts. This should in all justice be the very reason why their achievements should be highly rated, and not ignored, by historians of to-day.

Erasistratus, I am well aware, is a dim figure. Who among our modern giants of experimental medicine would survive if all his works were lost?

But wherever we catch a glimpse of Erasistratus through the backward mists of time, he appears as an experimental physiologist systematically applying ideas derived from the physics of his day to problems of health and disease in the human body. One has only to read through some of Galen's works to confirm this. Indeed it was just this enthusiasm which aroused the angry Galen in his turn to perform many of his experiments.

Galen's technical brilliance was mostly applied to experiments by ablation; the results of some of them, particularly those on the nervous system, were epoch-making. But the epoch they made did not begin until a century ago when Brown-Séquard, Schiff and others, followed them up.

Leonardo inaugurated physiological experiment by the method of producing models in glass – the *in vitro* method – wherein the conditions of the experiment can be varied under accurate control. He demonstrates perhaps most clearly of them all, the art of creative science, an art which was so evident in the inventive genius of such men as Claude Bernard and Louis Pasteur, in their determination to apply the sciences of physics and chemistry to medicine.

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