Nobel Lecture

Nobel Lecture, September 11, 1916

Some New Methods for Functional Testing of the Vestibular Apparatus and the Cerebellum

Ladies and Gentlemen! It gives me great pleasure to be giving the Nobel Lecture before you. In it I shall be reporting on the results of my research for which the Royal Caroline Institute - permit me here once again to give public expression of my deepest gratitude - has awarded me the Nobel Prize. Naturally I can only present a fraction of these results and I shall have to content myself with telling you briefly the history of those discoveries, the understanding of which only requires a minimum of specialist knowledge. For, as one becomes immersed in the material, the things which must be known for a proper comprehension of what follows become so numerous and complicated that it would almost certainly be impossible for the lay public to follow and I must regard as laymen, Ladies and Gentlemen, not only the many non-medical persons among you, but also the representatives of other branches of medical science whose presence here does me great honour. I have already given, on repeated occasions, a historical account of my discoveries. I must, therefore, ask the indulgence of those specialist colleagues, the Prize judges and the members of the Royal Caroline Institute who have found my work worthy of the highest scientific distinction if I say nothing which is new or interesting to them. This, if I have understood it aright, is not the purpose of the Nobel Lecture either, for it should serve far more to give the lay public a glimpse into the world of thought and work of the research scientist, just as the distinguished founder of this prize was a layman himself. To raise the general cultural level of mankind by promoting scientific work lay very close to the heart of Alfred Nobel. I shall ask this eminent gathering to regard my lecture from this standpoint.

I will start by describing to you the discovery of a new method of testing the apparatus of the semi-circular canals. As you will know, the inner ear, not only in humans but also in all vertebrates, consists of the cochlea for the purpose of hearing and the vestibulo-semi-circular canals. The anatomy of the vestibulo-semi-circular apparatus has been enormously developed here in Sweden by Gustaf Retzius whose wonderful work in this sphere I can show you here. You will see the manifold developments of the semi-circular canal apparatus in different classes of vertebrates. I can pass round anatomical preparations of this organ in man thanks to the kindness of the Director of the Otological Clinic, Professor G. Holmgren. Up until the 19th century there was a complete lack of knowledge of its function. The first to begin experimental investigations in this field was

the celebrated French physiologist Flourens. His investigations were published in 1825. Flourens thought that it would be possible to get an insight into the function of the semi-circular canal apparatus by destroying it. In fact, these experiments which were undertaken with pigeons, rabbits and other animals produced quite remarkable, constant and previously unknown disturbances. For instance, if the horizontal semi-circular canal was destroyed in a pigeon, it went on turning horizontally in a circle. If a vertical semi-circular canal was destroyed, the pigeon turned somersaults. Flourens has described the phenomena extremely well. But he did not give an explanation. In particular, he did not have the faintest idea that the animals were suffering from vertigo. For the well known symptoms of vertigo in humans are too different from those in animals for Flourens to have been able to see this connection. Also, the work of a great physiologist in Prague, Purkinje, was unknown to Flourens, although Purkinje was actually, in the same year, investigating the phenomena of vertigo in humans. Purkinje tried out his experiments partly on himself and partly on mentally sick persons, who, at that time, if they became violent were treated by being rotated in a cage until such time as the nausea thus induced made them quiet and manageable again. Purkinje has discovered the involuntary movements of the eye ball during vertigo, the nystagmus of the eyes, about which we shall be speaking a great deal. He has also proved the influence of the head position upon the vertigo symptoms and has shown that the vertigo arises in the head itself. He thought, it is true, that the brain itself was being directly stimulated by the rotation. He knew of Flourens's work. But strangely enough he too did not realize that Flourens's animals were suffering from vertigo, nor that in the spot where certain sensations arise there must be a sensory organ present which receives them. Like other research scientists of the 19th century, he had not yet penetrated far enough into epistemology. Even such an obvious idea as to observe an animal with vertigo or to rotate an animal did not occur to him, in spite of the fact that he conducted numerous vertigo experiments with human subjects and made frequent use of animal experiments. You can see from this how easily one can pass by within an inch of the truth.

As neither of these two great research scientists was able to find the solution to the mystery, it is small wonder that none of their contemporaries were able to do so either. Science stood still in this respect for nearly 40 years. Only in the year 1861 was a Frenchman, Ménière, able to take a bold step forward.

Méinière proceeded along totally different lines from his predecessors. He was an otologist and had observed from a purely clinical standpoint the frequent coincidence of vertigo, "Schwerhörigkeit" and tinnitus in cases with normal middle ear. The site of hearing was now known to be in the cochlea. Its destruction or impairment caused the tinnitus and the "Schwerhörigkeit". Vertigo, it was thought at the time, could only be caused by a disease of the cerebellum. He observed this kind of patient for years and saw absolutely no symptoms of brain disease. Apart from Flourens's experiments, the semi-circular canal apparatus which is connected with the cochlea was at that time thought to have no function. It was not known what the disease there might produce. Ménière now had the idea that the vertigo phenomena were symptoms of disease in the semi-circular canal apparatus and he now succeeded, where Flourens and Purkinje had failed, in seeing through the confusing diversity of the vertigo manifestations in humans and in animals

and recognizing that those animals whose semi-circular canals had been operated upon by Flourens had vertigo. This was the principle great achievement of the man who, unfortunately, did not survive to enjoy the fame of his discovery since he died in the same year. Ménière did not express himself as regards the importance of the semi-circular canal apparatus in normal life. The first to produce a theory on this was the German physiologist, Goltz, in 1870. He thought approximately as follows: if the destruction of the semi-circular canal apparatus gives rise to vertigo and imbalance, then the normal function of this apparatus must be to maintain equilibrium. And he formulated a theory as to how this might be so. I will not go into this theory here, since it was subsequently proved to be incorrect. But from this example you will see the chief importance of a working hypothesis. The interpretation of facts in a certain way stimulates other scientists' thoughts. The incorrectness and weaknesses of a theory cause other minds to formulate the problems more exactly and in this way scientific progress is made. In actual fact, we observe the spectacle not uncommon in the history of medicine, that only a few years later, in 1874, three men arrived all at the same time at a theory concerning the semi-circular canal apparatus which is even today, broadly speaking, correct. These were a general practitioner who is still alive, Dr. Josef Breuer in Vienna, the Viennese physicist and philosopher, Ernst Mach, who died last year and the American, Crum Brown, in Philadelphia. These three men arrived at the same result in very different ways. Breuer started by repeating Flourens's experiments with pigeons with improved technique and came directly to the conviction that movement of the fluid in the semi-circular canals, the endolymph, gave rise to the Flourens phenomena. He was, in addition, the first to put animals into rotation and proved thereby that the same phenomena which Flourens had produced by destruction of the semi-circular canals could be equally well produced by rotating the animal when the symptoms would be only transitory and harmless to it, the symptoms being, in fact, the result of rotatory vertigo. He also proved that when the semi-circular canals were destroyed on both sides, rotation no longer produced these symptoms. With this experiment he was the man who purposely took the first steps on the way towards establishing the function of the semi-circular canal apparatus. As a result of his experiments and of much physiological and anatomical deliberation, he came to the conclusion that the semi-circular canal apparatus is a sensory organ for the perception of rotary motion and that the phenomena of rotatory vertigo is the result of abnormally strong stimulation of this sensory organ. Mach set to work in quite a different way. First he established the mathematical equations for rotary movements. Then he made some investigations with human subjects to ascertain whether there was any evidence of a sensory organ capable of perceiving rotary motion. For as a thinker of the philosophical school he could not make the same mistake as Purkinje of imagining that the brain itself perceived directly its pulling as a result of rotation. Gradually, as a result of his deliberations, he was able to prove that all the other senses were incapable of producing the turning sensation. There remained only the semi-circular canal apparatus and he then showed that this, by virtue of its structure, was absolutely suited to the task of perceiving rotary movement. Crum Brown solved the problem in yet another way. He investigated a number of persons with regard to their vertigo symptoms and without much further thought he came directly to the assumption that the semi-circular canal mechanism must be the sensory organ capable of apprehending these quite specific sensations.

These are the founders of the theory of the semi-circular canal apparatus. Out of the large number of subsequent research scientists I can only name a few with the most outstanding achievements. Among the physiologists there is the Hungarian Högyes; Ewald, a pupil of Goltz, and among the clinicians Jansen, an otologist in Berlin. Högyes began by reexamining and modifying the experiments of Flourens and Breuer. He then set himself the task of establishing the site of the central mechanism governing the movements of the eyes, the nystagmus already referred to, which is set in motion by the movement of the endolymph. Here he was successful in the case of rabbits. He was able to show that the nystagmus mechanism is located in the parts of the brain between the entrance of the auditory nerve into the medulla oblongata and the corpora quadrigemina, and that the removal of other parts of the brain has no great influence on the course of this reflex. Hogyes also produced the best description of the symptoms after uni- and bilateral destruction of the semi-circular canals in animals and, in particular, proof that these symptoms are at their most violent immediately after the injury and then gradually subside, furthermore that the violent symptoms caused by the destruction of one side only can be reduced to a minimum by the destruction of the other side. He proved, in fact that the semi-circular canal on the one side influences that on the other side and that during stimulation they balance one another. It was Ewald who conducted the most exact experiments on the semi-circular apparatus in animals. He established an unquestionable connection between specifically directed head and eye movements of the animal with specifically directed movements of the endolymph in the semi-circular canals. It was he, also, who proved the extraordinarily marked and powerful influence of stimulation of the semi-circular canal apparatus upon the entire body musculature, thereby adding to the purely psychological theory of this organ an important new aspect, that of the tonic, reflex influence on the body muscles. Among the clinicians of this epoch, Jansen comes next in importance after Breuer and Mach. He was the first to discover the great significance of nystagmus of the eye as a symptom of disease of the semi-circular canal apparatus. He has given an extremely good description of the course of symptoms in human beings after destruction of the semi-circular canals, although he was, in fact, unaware that he was describing their destruction. He believed rather that he was referring to a special form of disease. Jansen also showed the great frequency with which diseases of the semi-circular canals occur in cases of suppuration of the middle ear and he was the first to remove by operation a suppurating semi-circular canal in human patients. In spite of the pioneer work of all these men, however, the whole field of diseases of the semi-circular canals in humans was veiled in obscurity. It was impossible to understand all the phenomena observed, for there was no real method for testing the function of the apparatus such as had long since been carried out for other sensory organs.

This is understandable because in the case of other sensory organs the test of function was easy to instigate. It was only necessary to arrange the various stimuli systematically and then, after exclusion of one of the sensory organs which occur everywhere in pairs, to test the other. This can be done with the eye, the auditory organ, the nose, taste and skin sensitivity. But this system of one-sided testing was impossible with the semi-circular canal apparatus.

The rotary method instigated by Breuer stimulated both sides at once and was, therefore, not satisfactory for clinical use where one-sided testing was nearly always required. The galvanic reaction method discovered by Purkinje and further studied by Hitzig and others did not give results which were suitable for clinical use, and this is still the case today. The caloric reaction method which I discovered was the first to bring light into this obscurity. Only after its discovery was a methodical examination of the function of the semi-circular canals made possible. Permit me now to tell you about the history of its discovery.

As a young otologist I worked in Professor Politzer's Clinic in Vienna. Among my patients there were many who required syringing of the ears. A number of them complained afterwards of vertigo. Obviously I examined their eyes and I noticed in doing this that there was nystagmus in a certain direction. I made a note of this. After a time, when I had collected about twenty of these observations, I compared them one with another and was amazed always to find the same note. I then realized that some general principle must be implied, but at the time I did not understand it. Chance came to my aid. One of my patients, whose ears I was syringing, said to me: "Doctor, I only get giddy when the water is not warm enough. When I do my own ears at home and use warm enough water I never get giddy." I then called the nurse and asked her to get me warmer water for the syringe. She maintained that it was already warm enough. I replied that if the patient found it too cold we should conform to his wish. The next time she brought me very hot water in the bowl. When I syringed the patient's ear he shouted: "But Doctor, this water is much too hot and now I am giddy again." I quickly observed his eyes and noticed that the nystagmus was in an exactly opposite direction from the previous one when cold water had been used. It came to me then in a flash that obviously the temperature of the water was responsible for the nystagmus. From this I immediately drew certain conclusions. If the temperature of the water was really responsible, then water at exactly body temperature should cause neither nystagmus nor vertigo. An experiment confirmed this conclusion. Furthermore, I said to myself, if it is the temperature of the water, nystagmus must be caused in normal cases also and not only in cases of suppurating ears. This I was also able to prove.

Because of my earlier research, I did not doubt for a second that the nystagmus was the result of a reflex action of the semi-circular canals. Hence, the further conclusion followed that if these were destroyed there would be no reflex action. I was able now to look among the abundant material available in the Vienna Otological Clinic for a suitable case. Before long, I found a case of severe suppuration of the middle ear, in which, even after continuous cold syringing, there was no nystagmus reaction. I diagnosed destruction of the labyrinth (or semi-circular canal mechanism) and an operation proved this to be correct. The importance of this reaction in the diagnosis of diseases of the inner ear was obvious. But there had now to be a series of cases in order to confirm its correctness. This was forthcoming. Afterwards I set myself to study the clinical value of this method of testing the semi-circular canal apparatus, using the caloric reaction as a control, while at the same time a clinic now had to be set up for diseases of the semi-circular canals. In

this a number of research scientists have co-operated and I must mention in particular, in addition to those of the Vienna school, the Stockholm Professor of Otology, Gunnar Holmgren. I had already recognized the importance of the caloric reaction and yet I could not explain it. In vain I reflected upon it. Then, one day, I had an idea. I remembered the bath water tank and my surprise, as a child, at finding the water immediately above the fire quite cold, whereas higher up, at the top, the tank was so hot that it burned ones finger. The labyrinth reminded me of a bath-water tank, i.e. a container filled with fluid. The temperature of the fluid is, of course, 37°C - body temperature. Suppose I spray one side of the container with cold water? What will happen? The water on this side of the tank will cool, of course, and, therefore, it will attain a higher specific weight than the surrounding water and will sink to the bottom of the container. Other water at body temperature will take its place. If I syringe the ear with hot water, on the other hand, the movement will be exactly the opposite. The movement of the fluid must change, however, when I alter the position of the container, and if I turn the container through 180°, it must change in exactly the opposite direction. Immediately I was able to envisage the kind of test which would serve as *experimentum crucis* for this theory. If, in two head positions differing from one another by 180°, it is possible to obtain nystagmus in opposite directions by syringing, whether with hot or cold fluid, then this theory must be correct. I went to the clinic and arranged the experiment and, in fact, the hoped-for result showed itself very clearly. Two head positions differing by 180° show nystagmus in exactly opposite directions. The theory of the reaction was now established and it agreed absolutely with the theory of both Breuer and Mach which had recognized the movements of the endolymph, the fluid contained in the semi-circular canals, as being the cause of stimulation in them.

I will not proceed any further with this line of thought, but, on the other hand, mention my discoveries with regard to localization in the cerebellum. The investigations of Ramón y Cajal, the Spanish histologist, who is also a Nobel Prize winner, have shown that each fibre of the nervus vestibularis, i.e. the semi-circular canal nerve, divides into a number of branches at the point of entry into the brain. One branch leads towards a group of cells which are in direct connection with the ganglia cells of the central eye muscles and we can understand, therefore, why stimulation of the semi-circular canal causes nystagmus of the eyes. One branch, however, goes into the cerebellum and divides into a series of branches leading to the two side portions of the cerebellum, the so-called cerebellar hemispheres, and to the central portion of the cerebellum, the vermis. Admittedly Ramón y Cajal only carried out these investigations on the embryos of quite small animals. His methods are not applicable to larger animals and, in particular, to human beings. Analogy, however, allowed me to conclude that in humans also there must be a connection between the semi-circular canal nerve and the cerebellum. Up until now, I have only mentioned among the symptoms caused by vertigo the turning sensation and the eye nystagmus. But you are all aware of the other symptoms, in particular the effect upon the trunk muscles caused by disturbances of equilibrium. I cannot give you all the reasons here which led me to conclude that this influence upon the muscular apparatus of the whole body comes from the semi-circular canals via the brain, but the book by the Dutch anatomist, Louis Balk, on the cerebellum in mammals, which appeared in 1906, gave me some very valuable pointers. In this book Balk tells us roughly what follows.

The efforts of the physiologists have shown us that the cerebellum has something to do with the innervation of the muscular apparatus. In vertebrates we find that the muscular apparatus of the body is very different in different classes of animal. For instance, the giraffe has an enormously long and mobile neck, the mole has a very short and quite immobile neck. Bolk decided, therefore, that obviously the parts of the brain which take care of he neck muscles in these animals must be developed in quite a different way. He examined the cerebellum in both these species and noticed the extremely striking formation of a certain portion of it in the giraffe which was almost completely missing in the mole. From this Balk concluded that this particular portion was concerned with the innervation of the neck muscles. In a similar way coming to conclusions, he arrived at quite definite localizations for all parts of the cerebellum and, what is particularly important for us, that the muscular apparatus of the upper and lower extremities was represented in the side portions of the cerebellum and that of the trunk in the centre portion. Testing the influence of the semi-circular canal apparatus on the trunk muscles is very simple. The patient is asked to stand or walk and disturbances of equilibrium, deviation from a straight line, are noted when the semi-circular canal is stimulated, e.g. by cold water. The effect of stimulation upon the extremities, e.g. the upper extremities, is also very easily demonstrated. The patient is asked to stretch his arm straight out and keep it quite still. Without stimulation of the semi-circular canal mechanism this is done without difficulty. If, however, the ear, let us say the right ear, is syringed with cold water, the patient's arm will move slowly towards the right without his being aware of it. It can easily be shown that this deviation of movement will also occur with the left upper extremity and also with both legs. This experiment is the most certain way of demonstrating the direct influence on the muscular mechanism. Usually, however, I employ the so-called pointing test. This is as follows: The patient is asked to close his eyes and touch the doctor's finger with his own index finger, then, still keeping the arm outstretched, to lower it to knee-level, then raise it again and touch the doctor's finger once more. In a normal state, with very little practice, this can be done without difficulty. After stimulation of the semi-circular canal, i.e. after syringing of the right ear with cold water, a normal subject will not be able to touch the doctor's finger, but will pass it on the right. The direction of this deviation will differ according to the direction of the nystagmus and is always in an opposite direction to the nystagmus. Should, for instance, nystagmus occur to the right, the finger will pass the target to the left. If nystagmus occurs in a downward direction, then deviation will be upwards. Nystagmus in an upward direction will be associated with deviation below the target. The reactions always affect all four extremities and the whole muscular apparatus.

I was now successful in proving that a direction of movement is localized in the cerebellum. For I found cases in which the reaction of the extremities was missing in one direction only (on the side of the cerebellar hemisphere which was diseased) whereas the reaction of the extremities on the other, healthy side and all the other reactions in the extremities on the diseased side were normal. This indicated that the nerve cells and nerve fibres concerned with reaction in a certain direction must lie close together within the cerebellar hemisphere. Close investigations, however, proved something more namely that within such a centre there was also localization with regard to joints. For I found cases where deviation only occurred in a certain joint of the extremity, while all other

reactions were normal. For instance, failure in the pointing test only occurred in the shoulder joint of the right arm towards the left, whereas the elbow joint of the right arm, the right wrist, the hip joint of the right leg and all the joints of the left side showed a normal reaction to the left when there was nystagmus to the right.

The investigations also proved that there were many cases of spontaneous deviation, i.e. *cases where there had been no stimulation of the semi-circular canal apparatus*. Let us assume, for instance, that in one case the right shoulder joint deviates to the right. If in such a case I tested the reactions while there was a nystagmus to the right, the right shoulder joint showed no deviation to the left but pointed correctly, whereas the other extremities and joints showed the typical deviation to the left. From an accumulation of such experiments I came to an absolutely definite concept of the method of action of the cerebellum. I assumed the presence in the cerebellum of four centres in which the muscular apparatus was arranged firstly according to direction and within these centres according to articulation - one centre for the right, one for the left, one for an upwards and one for a downwards direction. In normal people, as long as there is no stimulation of the semi-circular canals, these four centers provide a certain tension, called tonus, for the muscles during movement of the extremities. Each pair of these centres acts like two reins between which the arm, for instance, moves. If both reins are spanned equally tightly, the arm moves, without any deviation, towards the required position. I might, however, pull one rein harder than the other. This happens if I stimulate the semi-circular canal mechanism. If I produce a nystagmus to the left, this is equivalent to pulling on the right-hand rein and, therefore, the arm deviates to the right. But I can also bring about a deviation of the right arm to the right if I cut the left-hand rein, for then the tension of the right-hand rein which is already present without any stimulation of the semi-circular canal will make itself felt and will pull the right arm spontaneously to the right. If I now attempt to tighten the left-hand rein, this is now, of course, impossible since it has been cut. All I can do is to relax the right-hand rein completely and then the arm will once again point correctly.

Let us now translate this comparison into medical language. Disease of a certain centre, for instance the centre for the tonus of the right arm towards the left, causes the right arm to deviate to the right without any stimulation of the semi-circular canal mechanism: there is spontaneous deviation in the pointing test to the right. If I produce a nystagmus to the right, i.e. if I attempt to stimulate the tonus centre for the right arm to the left, I am unsuccessful, for this centre is diseased and is not functioning. All I can do is to inhibit the tonus centre for the right arm to the right completely and thus obtain correct pointing. This is the chief interpretation of the physiology and pathology of the cerebellum which I profess. There are many other illustrations of it which I have not time to mention here.

Finally, I must mention one more experiment which I was the first to use with human subjects and which seems to me to give important results for our study of localization in the brain. It is an experiment which the physiologist W. Trendelenburg first used on apes. Trendelenburg exposed the dura mater over the right cerebral hemisphere just at that spot which experience has shown to be the movement centre for the left hand. The localization of muscles in the cerebrum has been very exactly defined, thanks to the work of a number

of research scientists. Over this spot Trendelenburg fastened a capsule through which he could pour iced water. The animal was then put into the cage where it soon recovered from the narcosis and began to move around the cage and eat, etc. Trendelenburg, who was standing outside the cage, now suddenly poured iced water through the capsule. Instantly the ape's left arm fell paralysed to its side, without, however, the animal noticing. It went on quite happily eating its turnips or climbing around in the cage, but now, instead of using all four extremities, it only used three, for the left arm was paralysed. This paralysing effect lasted as long as the cooling effect of the iced water on the cerebral cortex. If Trendelenburg exchanged iced water for water at body temperature, the left arm at once came into use again. The animal began to use it for climbing, eating, etc. just as though it had not been paralysed a few seconds earlier. Trendelenburg was able to repeat this experiment over and over again without the slightest damage being shown, and no paralysis remained. This very interesting and important experiment was pointed out to me by Professor Kolmer and I decided at once to use it upon human subjects. Quite by chance, a patient was available with a healed cere-bellar abscess whose life I had saved by operation. Here the dura mater of the cerebellum was exposed immediately underneath the skin and I thought I would try to cool this spot on the skin in order to paralyse temporarily the cerebellum lying beneath it. As a result of the experiment with apes, it was to be assumed that no harm would come to the patient from this procedure. I decided that although the cooling of the skin might not be very pleasant, I could reasonably expose this patient, whose life I had saved, to this small discomfort in order to achieve scientific progress which would benefit the whole of humanity. The experiment was intended to prove two things: (1) the localization in the cere-bellar cortex; (2) the practicability of the cooling method in research into brain function in living human beings. The experiment fulfilled my expectations completely. For the cooling process I used ethyl chloride, the fluid often used in surgery to anaesthetize parts of the skin when small operations are to be carried out here. I froze the skin over the right side of the cerebellum and the effect of this was immediately visible. The right arm deviated immediately to the right and, for the duration of the cooling period, there was no pointing reaction to the left when I produced a nystagmus to the right in the subject. I had, therefore, hit the exact position of the tonus centre for the right-shoulder joint to the left. The momentary paralysis in the patient showed itself by the deviation of the shoulder joint in the right arm to the right during pointing and in the non-appearance of the pointing reaction to the left. As soon as I had proved this and, of course, also the normal pointing action and reactions in all other extremities and joints, I stopped the experiment. Two minutes later the right arm was pointing normally and the reaction to the left appeared. The patient made no complaint at all about the experiment. I repeated it on the same subject approximately twelve times, always with the same result. It was also carried out on a patient in Professor Voss's Clinic in Frankfurt, where Dr. Hirsch, who was at that time an assistant in the Otological Clinic, used it repeatedly and always with the same success. I also used it successfully on a patient in the Passow Clinic in Berlin in the presence of Professor Beyer and Professor Lewandowsky. During my present stay in Denmark Professor Schmiegelow told me that it had several times been used with success on one of his patients. One can, therefore, say with confidence (1) that localization in this spot is correct, and (2) that the experiment can be used on a large scale without any danger to the patient. During the present war, and afterwards, there will be

numerous opportunities of using the experiment, for the instances of head injuries arecountless, in which, after healing of the wounds, the dura mater will be covered with only a thin layer of skin. I am convinced that people with such wounds will be quite ready to co-operate in a safe and painless experiment in the interests of humanity as a whole.

From *Nobel Lectures, Physiology or Medicine 1901-1921*, Elsevier Publishing Company, Amsterdam, 1967