1983 Ernst was awarded a gold medal of the Society of Magnetic Resonance in Medicine. In 1985 he was honoured with an honorary doctorate by ETH Lausanne, and was awarded the Marcel-Benoist Prize in 1986. During 1988 he was R. B. Woodward visiting professor at Harvard University, USA. In 1991 he was awarded the prestigious Wolf Prize. Ernst has visited India twice in recent years, to lecture at the Tata Institute of Fundamental Research, Bombay, in 1984 and the Indian Institute of Science, Bangalore, in 1986.

Ernst is one of those fine people who combine humility with knowledge. He is an extremely polite person and a thorough gentleman. This is exemplified by his characteristic style of putting the names of all his associates prior to his own name in all his publications even though his own personal contribution may be the largest. He also has the rare quality of combining perfection with polite persuasion. Like all Swiss, he loves mountains and is an expert guide. He has deep interest in Western classical music and is a lover of fine arts. He has a large collection of Tibetan *tankas* (religious scroll paintings), and his wife once remarked (when they did not own a car in the early seventies) that whenever they had enough money (to buy a car) he went and bought a painting. I wonder what he will do with the Nobel money!

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Membrane ion channels singled out

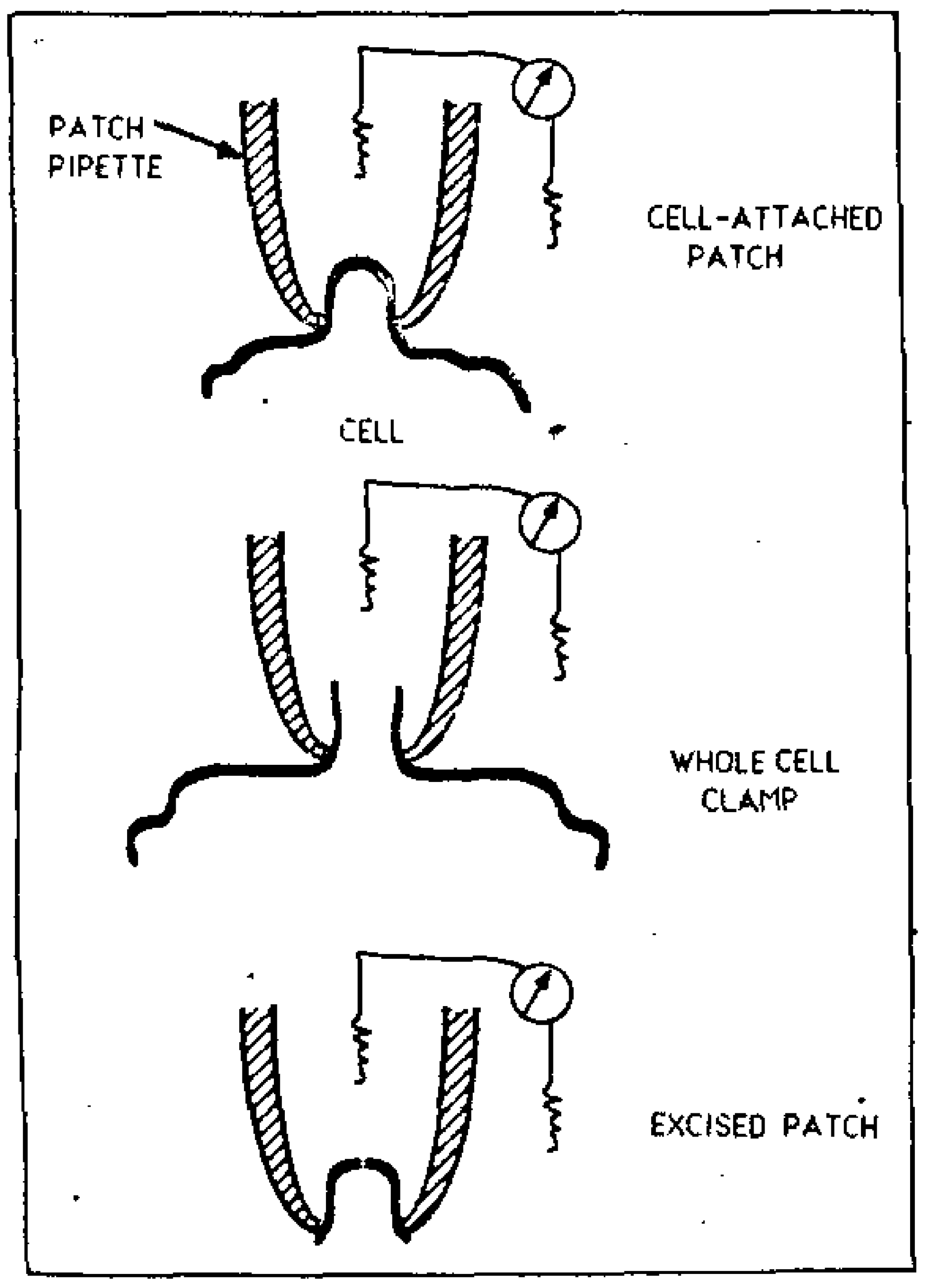
This year's Nobel prize for physiology or medicine celebrates a technique that allows detailed study of membrane function.

The study of ion transport across biological membranes is a paradoxically old field: Nasse described the exchange of anions across red blood cell membranes a decade before Arrhenius proposed his ionic theory. Nasse actually talked of the acids rather than anions *per se*. The area has remained quirky ever since, with the study of ion channels proceeding full steam ahead at a time when the existence of the biological membrane itself was under debate. It has had its share of luminaries, such as Luigi Galvani who demonstrated that electrical stimulation could mimic nervous excitation for muscle contraction, Hodgkin and Huxley who dissected the ionic components of the action potentials of nerve, and, more recently, Neher and Sakmann who devised techniques to study the movement of ions through individual channels in biological membranes.

The biological membrane is oil-like (lipophilic) in composition and presents a formidable barrier to passage of charged species like sodium or calcium ions. Most membranes have structures that form molecular conduits through the membrane, filled with water, which permit easy passage of ions. The channels responsible for the action potential in nerve are capable of passing many millions of ions per second while retaining the ability to distinguish between species as similar as sodium and potassium ions. The traditional method of studying these molecules was to insert electrodes into cells and monitor the passage of ions through the entire ensemble of channels in the membrane as an electrical signal that could be detected with appropriate electronics (currents of the order of nanoamperes to microamperes were seen).

A very few channels could be purified to homogeneity and incorporated into artificial bilayer lipid membranes (BLMs). Electrodes could then be placed in the aqueous compartments on either side of the BLM and currents measured. This limited study to a few well-characterized membrane channel proteins and was carried out in an artificial setting. However, by playing around with the concentration of the channels in the BLM, it was sometimes possible to observe transport through a single open channel at a time (single-channel currents). This provided a wealth of information that forms the basis of our current thinking about the molecules that make up such channels. Neher and Sakmann pioneered a method (the patch clamp) for study, at a similar resolution, of channels in their native setting.

The patch-clamp technique involves pressing a pipette against a cell membrane and generating a seal that is tight enough to prevent the passage of ions between the pipette and the membrane. If an electrode is introduced into the pipette, the only current that can be detected will be that passing through



the patch of membrane at the mouth of the pipette (see figure). This often involves sucking in a portion of the membrane into the pipette. This configuration is called the cell-attached patch or on-cell patch. Sucking hard enough to break the small patch within the pipette generates a whole-cell patch. Alternatively, the patch can be pulled off the cell, and is called the excised patch or inside-out patch as this exposes the portion of the membrane that is normally within the cell. Thus both surfaces of the membrane are available for treatment with reagents of interest. Again, for suitable combinations of membrane area and channel density, it is possible to carry out single-channel studies[1,2].

Another application of the technique is the measurement of the so-called gating currents. Many ion channels are regulated by transmembrane potential, which implies that part of their structure must include a voltage sensor. It has been postulated that this voltage sensor moves in response to changes in the transmembrane potential and that this movement is then tied in (by as yet poorly understood mechanisms) with channel opening and closing (gating). Since the voltage sensor is likely to be charged (or a dipole), this movement should be detected as a current (the gating current). Unlike the ionic currents flowing through the open channel, which are of the order of 10^7 ions per sec, the gating current may be only a few charges moving per gating event. This may be swamped by the current involved in charging up the membrane capacitance. By using a small patch crammed with channels, one can minimize the capacitative current. By using ions that will not pass through the channel one can eliminate the ionic currents and study the gating currents. The BLM has an enormous area of membrane and so is not really well suited for this type of study. Fred Sigworth, who was a postdoctoral fellow with Neher and is now at Yale, is currently attempting to work out the steps in channel opening using cloned potassium channels.

Since the invention of the patch clamp, Sakmann has concentrated on the study of ion channels whose genes have been cloned[3]: the acetylcholine receptor[4], in particular. Neher, on the other hand, has been interested in the study of secretion processes[5]. Secretion involves the fusion of small secretory vesicles with the plasma membrane, which increases the area of the plasma membrane and can therefore be monitored as an increase in capacitance. In addition, calcium, which is thought to be important in these processes, can be monitored using a suitable dye. Neher is currently trying to look at the variation in concentration of calcium using dyes and microscopy; fusion of vesicles by monitoring capacitance; and formation of channels during the fusion process by monitoring conductance with a whole-cell patch simultaneously.

The introduction of the patch-clamp technique has made it possible to identify and study channels in a wide variety of tissues with little biochemical purification. The characterization of novel ionic currents has become a growth industry. The technique has found wide application in the study of channels whose genes have been cloned, including the sodium and potassium channels involved in the action potential of nerve, calcium channels of various hues, and the acetylcholine receptor that is Sakmann's current interest. Diabetes, epilepsy, cystic fibrosis and certain types of heart disease have all been shown to be associated with defects in regulation of ion transport. The gene responsible for cystic fibrosis has been cloned and shown to encode a chloride channel. Indeed, many more channels have been studied since the introduction of the patch clamp than had been identified in the period between Nasse and Neher/Sakmann—a testimonal to the enormous impact their work has had. It is fitting that their contributions to medicine and physiology have been recognized by the Nobel committee this year.

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Seismically vulnerable region hit again

The earthquake that hit the Garhwal region in the western Uttar Pradesh hills in the early hours of 20 October was another in a series of earthquakes that have occurred in this area (see box next page). The region, located on the interplate boundary where the Indian Plate is thrusting against the Eurasian Plate, is vulnerable to the occurrence of earthquakes.

Plate tectonics envisages the movement of lithospheric plates against one another as the cause of building up of stresses. These stresses are released as earthquakes. The collision of plates may also have caused the formation of some