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EDITORIAL

Technical Innovation of Ervin G Erdös: a Mechanical Transducer for Isotonic Muscle Contractions

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I wrote on the renowned pharmacologist Professor Ervin G Erdös and his scientific opus in my reminiscence article written on the occasion of his death in 2019.[1] When I attended the Fourth International Congress in Pharmacology in Basel in 1969, Dr Ervin G Erdös invited me to join his laboratory. Thus, in April 1970, I arrived in Oklahoma City as a Fulbright Fellow to work with him for two years. Later on, as a visiting scientist I frequently worked in his research laboratories in Dallas and Chicago and we shared research interests through visits across the Atlantic between the former Yugoslavia and the United States.[2, 3]

Principles of bioassay

In Sarajevo, for my daily research, I used a bioassay with frog *rectus abdominis* muscle to determine acetylcholine level in various regions of the pigeon's brain. With this tool, I developed a method to estimate amounts of "free" and "bound" acetylcholine and Ulf Svante von Euler[4] suggested that I should publish these findings in a good international research journal.[5]

Let me explain the principle of bioassay. It is an analytical method for determination of the relative strength (concentration or potency) of a substance by comparing its effect on a test organism (living animal, cells or tissues) with that of a standard preparation. Bioassays are used in pharmacology mainly to determine the concentrations of hormones or drugs, eg biologically active peptides, acetylcholine, catecholamines, prostaglandins, histamine and prostacyclin. However, there are other forms of bioassay in which one can use isolated tissues and determine actions of their nerves, such as the nerve to the diaphragm from rats. Bioassays may also be done *in vivo* in individual humans. The assessment of drug effects in humans is designated by clinical pharmacologists as a clinical trial. Such trials often require hundreds or sometimes thousands of patients in order to test efficacy and safety of any new drug before it can be marketed. If the human investigations produce unexpected results, quite different of those obtained in the animal experiments the trials must be redesigned, to examine why and how this occurred. There are many examples of how such discoveries resulted in new clinically useful medications (eg, discovery antihypertensive effect of beta-adrenergic blocking agents).[6] Accordingly, the pharmacologists have the bioassays, as a tool, which help them in the discovery process.

How bioassay became a useful tool

In 1903, Rudolph Magnus, a German pharmacologist and physiologist, suspended an isolated por-

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tion of smooth muscle in a chamber containing nutrient fluids and measured changes in tissue tone.[7] Sir Henry Dale, an English pharmacologist and physiologist, improved upon this with specifically designed organ baths (Figure 1) which are much like the ones used today. To record changes of isotonic pressure in contractile tissues researchers attached a piece of thread to one end of a strip of isolated tissue and attached the other end to hold it upright within an oxygenated organ bath; the thread was then connected to a stylus that would scratch a smoked sheet of paper wrapped around the kymograph drum (Figure 2). The smoked drum would turn to record the contraction or relaxation of a lever connected to the smooth muscle organ with time. At the end of the experiment, recordings were preserved by immersing the paper in a liquid shellac fixative and drying them. This bioassay was an extraordinarily laborious process, although it was used for many years to measure amounts of biologically active substances and it featured prominently in many important studies of that time.

The bioassay uses strips of various muscles (eg, frog *rectus abdominis*, rabbit aorta, rat uterus, rat colon and guinea pig ileum) for detection and quantification of minute quantities of biologically active substances. John Vane, who won a Nobel Prize in Physiology and Medicine in 1982, is among those scientists who used a special modification of the bioassay which perfused the lungs from a guinea pig with Krebs' solution and superfused a rat colon with the effluent. With these studies he showed the conversion of inactive de-

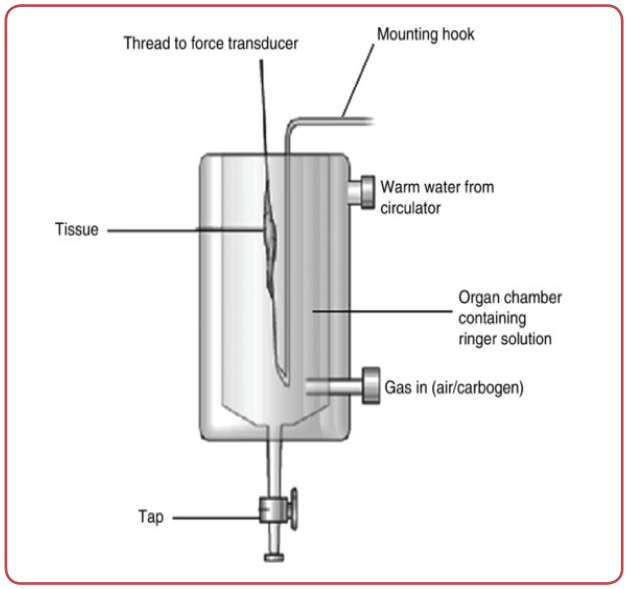

Figure 1: Organ bath for isolated muscle preparations

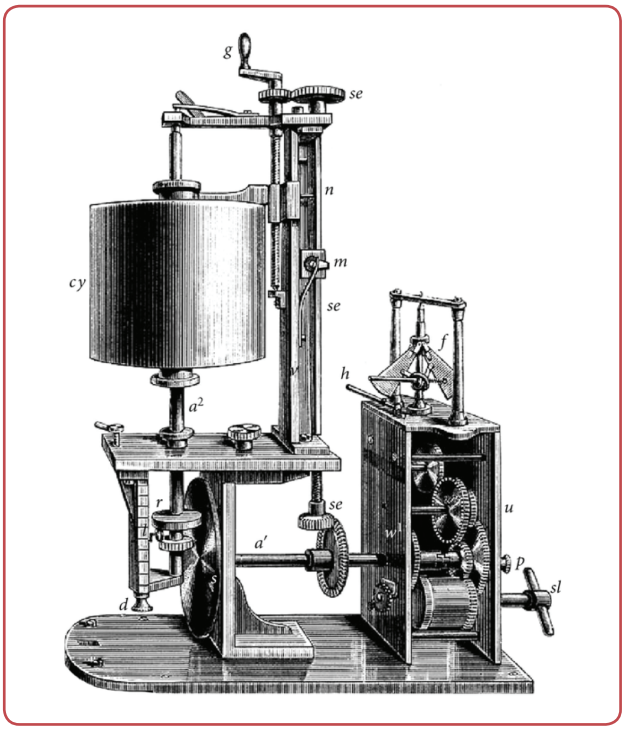

Figure 2: Ludwig's original kymograph

capeptide angiotensin I to very biologically active octapeptide, angiotensin II.[8] Such studies showed that the lungs have an important metabolic function; one that has become a field of research of its own.

Dr Erdös' laboratory surprised me

When in 1970 I watched a technician, Ms Deborah Downs, in Dr Erdös' Oklahoma laboratory doing a bioassay with a strip of rat uterus, I was astonished. She explained that this instrument, composed of a transducer and an electronic recorder (Figure 2), was Dr Erdös' invention and it was described in a paper published in the *Journal of Applied Physiology* in 1962.[9] Later on, in the Dr Erdös' laboratory (at first in Oklahoma City, then in Dallas and finally in Chicago) I used this original instrument and we published the data in several journals. Soon, miniaturised electronic devices for registration of isotonic and isometric muscle contractions became commercially available and widely used in many laboratories. The kymographs became history. We all marvelled this instrument, originally invented in the 1840s by Carl Ludwig, a German physiologist, to monitor blood pressure in animals and only later used for the bioassay. Now, after more than half a century, thanks to Dr Erdös invention, we had a valuable laboratory instrument to replace those smoky kymographs.

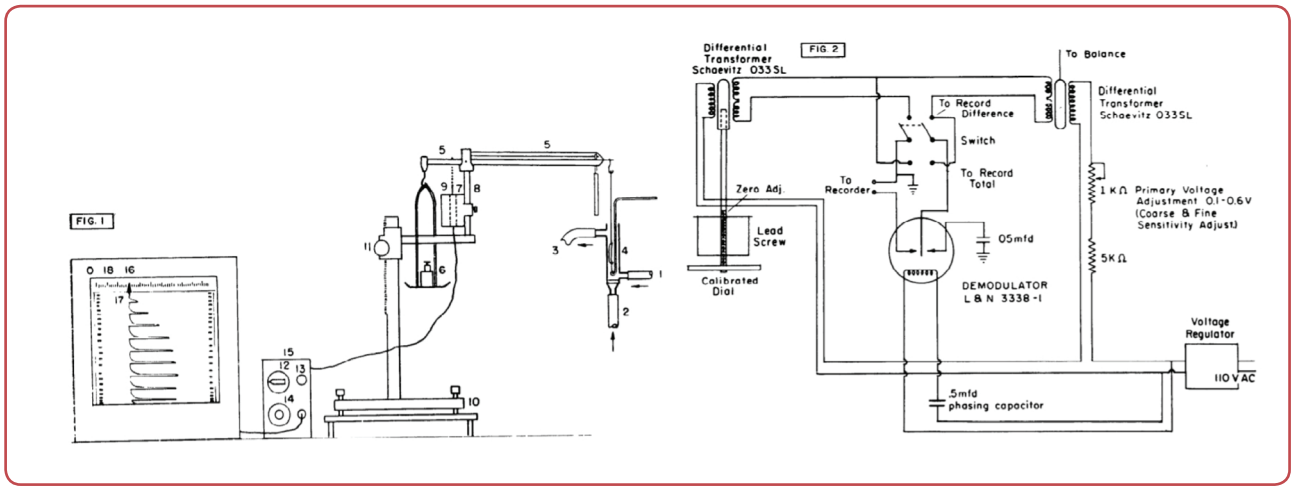

Figure 3: Schematic presentation of the first transducer (invented by Ervin G. Erdös) and electronic recording for isotonic contractions of smooth muscles. FIG. 1. Instrument for recording contractions of smooth muscles. 1 - inlet for Tyrode's or De-Jalon's solution; 2 - inlet for oxygen; 3 - outlet; 4 - muscle bath; 5 - balance arm; 6 - balance pan; 7 - differential transformer; 8 - balance support; 9 - flexible copper wire; 10 - balance stand; 11 - adjustable balance support; 12 - fine sensitivity adjustment; 13 - coarse sensitivity adjustment; 14 - zero adjustment; 15 - demodulator box; 16 - recorder; 17 - recording pen; 18 - sensitivity control on recorder. FIG. 2. Electrical circuit diagram.

A new technique for registering contractile responses of the isolated tissues

Could we ever expect that the mechanical sensors would be replaced? In order to avoid the tissue damage caused by the hooks or threads used with mechanical transducers and to obtain recording of contractions by monitoring the inner pressure, a new method used to measure blood vessel rings and other luminal organs, such as the rat trachea, blood vessels and uterus.[10] This method, using less complicated equipment (transducers, classic organ-bath, etc.) is faster and less expensive for recording contractile responses. However, it is hard to predict the next-generation tool for measuring the contractile effects of drugs on various isolated tissues.

Acknowledgements

None.

Conflict of interest

None.

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