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O EKSPERIMENTALNOM TREMORU

1 — 3. APRIL 1971. GODINE

Urednik
PAVEL ŠTERN,
redovni član Akademije nauka i umjetnosti
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ANDRÉ BARBEAU

SYMPOSIUM TREMENS*

Having been assigned the difficult task of summarizing this very interesting Symposium I have chosen to avoid the pittfalls of thorough and systematic review, by elaborating on what is definitely my own biased outlook on the mechanism of tremor, and incorporating what I think I have learned during these last two days. All of us came to the historic City of Sarajevo, at the invitation of Professor. P. Stern, who has been concerned with these problems for many, many years. We came to learn and to talk, and to think about tremor. To all intents and purposes what is tremor? What do we know now and what must we study in more details in the years to come?

To the clinican, tremor is an alternate contraction of flexors and extensors around a more or less fixed joint. It is endowed with specific rates and amplitudes which can be described and measured, but which change under special conditions. These must also be described, analysed and catalogued. Not all tremor is of parkinsonian origin and the laboratory investigator must avoid the errors of many clinicians. It is not yet clear in my mind what the relationship is between the tremor induced in animals by oxotremorine and that seen in patients. Shivering is not the rest tremor of Parkinson's disease, nor is it the intention tremor of cerebellar disorders! The only experimental tremor I have seen in animals which in some ways resembles parkinsonian tremor, is that induced by Reserpine.

In the end, the rate and amplitude of tremor must be organized and controlled at the periphery. Its final manifestation is in the coordinated action of alpha and gamma cells in the spinal cord and as they innervate the primary muscle spindle endings. We heard of the importance of that mechanism during this meeting *(Schäfer)*. If there is no doubt about the sensory input modulation at this level, it probably cannot influence the actual generation of tremor. Approaches to this general problem have been presented in studies of the blink reflex *(Gregorič)*, of tendon jerks and of controlled afferent inflows *(Dimitrijević)*

* This unusual title is adopted because of the chosen topic but also to remind us of the state of tremulousness, common to the other well known entity with a similar name, in which the speaker found himself before delivering this summary of the meeting.

and in therapeutic attempts involving low frequency muscular electrostimulation *(Jušić)*.

The true tremorigenic center is then situated above the monosynaptic reflex arc. Many levels of the neuraxis must be considered in the search for the so-called »pacemaker«. During this meeting we heard of the results of sections of the spinal cord in curare-induced shivering *(Ten Bruggencate)*. At an other level we were told of studies on the electrical activity of the cortex as it relates to tremor and as it is modified by parkinsonian drugs *(Tóth)* or adrenergic and cholinergic influences *(Bernard)*. An overview of drug induced rigidity and tremor was presented by *Jurna*. This author reminded us of the very important physiological observation that rigidity is abolished by removal of the striatum and that tremor produced by oxotremorine is of the gamma type while that induced by Reserpine is of the alpha type.

The only areas of the brain where independent firing cells with an *intrinsic* rhythm have been found in monkeys or in human stereotaxic studies, have been the posterior part of the ventrolateral nucleus of the thalamus and some components of the underlying subthalamic area *(Struppler)*. This area is the most important target for a successful surgical approach to rest, postural or intention tremor. These cells which we, somewhat facetiously, have called »pulsating«, receive important afferents from the cerebellum, the brain stem and the basal ganglia. The possible role of serotonin components in the brain stem output of the rubro-olivo-dentato-rubral loop of Poirier have been emphasized by us. We feel that damage to this possible serotoninergic pathway may result in hyperreactivity of the so-called »pulsating« cells. In this respect sleep studies carried out during L-DOPA treatment *(Kendel)* are particularly instructive, since tremor at night only appears during R. E. M. or unsynchronized sleep. This recalls the important investigations of Jouvet and his school on the role of serotonin in this system.

The other main input to the »pulsating« cells is from the basal ganglia. These nuclei, whose many pathways were thoroughly reviewed by *Gluhbegović*, may even be in some sort of an anatomical relationship to exterior configurations of the skull *(Hadžiselimović)*. At any rate they play mainly the role of a filter in sensory-motor integration. In this basic function, dopamine plays an important role.

Thus introduced, the relationships between the many striatal putative neurotransmitters which Otto Loewi studied so long ago *(Navratil)*, were thoroughly reviewed during this Symposium. *Potkonjak* reported experiments in which she relates brain levels of acetylcholine (ACh) and clinical rigidity induced by fluphenazine. There is now almost total agreement that tremor can be correlated with the levels of brain acetylcholine *(Oelszner)*, and more accurately with ACh release (whose mechanism was studied in detail by *Vizi*) or the state of stimulation and saturation of muscarinic ACh receptors. The emphasis obviously now has to be placed at the level of the *receptor*, the neglected component of this system. The mechanisms of sensitivity and/or of tolerance of these receptors to various drugs must be investigated, as was well done after oxotremorine by *Huković* and by *György*. The elegant model

proposed by *Župančić* for the membrane-bound acetylcholinesterase of the cholinergic receptor should be the basis for many more important kinetic studies.

We would like to propose, as an area of potential reward, that the so-called »pulsating« cells of the thalamus and subthalamus be separated by the specific single cell isolation techniques (described in this Symposium by *Pavlin*) and that the molecular pharmacology of their many receptors be studied along the lines proposed by *Župančić*. We would suspect that it will be found that the same cell can have specific receptors for many transmitters and that, somehow, the interaction between the membrane activities of these receptors will account for the rhythmic intrinsic properties of these cells. Only when we visualize the molecular basis of this activity will we truly understand the mechanism of tremor and will we be able to rationalize therapeutic attempts.

Another important aspect of the present Symposium has been the emphasis given to the role of trace metals in the production of various forms of tremor. This is understandable, given the long-standing interest in this subject of our host. Professor *Stern* reviewed in detail the experimental models of extrapyramidal diseases, particularly the role of iron and of copper and their mechanism of action at cellular and enzymatic levels. We personally have stressed the fact that it is more likely that these substances act through slow modifications (deficiency or loading) and that their effect on symptoms is through reaction of underlying amine imbalances, particularly in the striatum. Trace metals have again been studied in various extrapyramidal entities, confirming the iron and copper changes previously reported in Wilson's disease and Huntington's Chorea and adding important new observations on possible abnormalities of aluminium in these illnesses (*Bokonjić*). We reported how iron or chronic mangenesa loading, or a chronic magnesium deficiency, could modify the striatal dopamine content, and *Stanković* described how manganese treatment affects cholinesterase activity in total brain and basal ganglia of rats.

If such studies on trace metals and electrolytes offer possibilities towards the eventual understanding of the pathogenesis of tremor, we cannot say that the present has been forgotten because of that emphasis. We were gratified to hear of the results of therapeutic trials with Amantadine *(Schnieden)* and with L-DOPA (*Zec*), although in both cases the effect on tremor was not as marked as that on other symptoms.

At the end of these long but fruitful sessions we schould perhaps remind ourselves of some simple clinical and physiological truths: *tremor is only a symptom, it is not a disease:* If we have yesterday and today placed considerable importance on this manifestation, it should not obscure the fact that there may be many causes of tremor. It is even possible to change tremor into chorea or dystonia, or chorea into tremor, simply by modifying the underlying precarious balance between brain neurotransmitters, as every clinician who has used L-DOPA in Parkinson's disease or Fluphenazine in Huntington's Chorea could tell you.

Thus if today we understand better the symptom *TREMOR* and its physiology, we have not moved any closer to visualizing the etiology

of any diseases where tremor is present. Perhaps the investigation of trace metals may, in this way, be more important on the long run. Again our host would have manifested his scientific intuition in choosing this subject of study many years before most of us.

It is impossible to close such a Symposium without thanking, from the bottom of my heart, and with the certainty that the feeling is shared by all, our humble and so sympathetic Professor P. Štern. To him, to his ever smiling staff, to the Academy of Science and Art of Bosnia and Herzegovina, go our thanks for this most interesting Symposium on Experimental Tremor.

A. BARBEAU

SIMPOZIUM TREMENS

KRATAK SADRŽAJ

Sumirajući i spominjući sve autore — učesnike Simpozijuma, Barbeau je zahvalio Akademiji nauka i umjetnosti BiH i prof. Šternu za organizaciju Simpozijuma o eksperimentalnom tremoru. Postoje razni tremori, nije svaki tremor parkinsonske prirode, postoje mnogi uzroci tremora. Moguće je mijenjati tremor u horeu ili distoniju, ili obratno. Finalna manifestacija tremora je koordinirano djelovanje alfa- i gama-stanica. Tremor izazvan oksotremorinom je gama-tipa, a onaj izazvan reserpinom je alfa-tipa. Jedini eksperimentalni tremor koji je on vidio kod životinja i koji sliči parkinsonskom tremoru je onaj izazvan reserpinom.

Istinski tremogeni centar, »pacemaker« ili pulzirajuće stanice locirani su u posteriornom dijelu ventro-lateralnog nukleusa. Oštećenje serotoninskog puta prema pulzirajućim stanicama može rezultirati hiperaktivitetom pulzirajućih stanica. Acetilholin u mozgu ili, bolje reći, oslobađanje acetilholina, njegovo vezivanje na receptore, kinetičke studije odnosa acetilholin — receptori na pulzirajućim stanicama — mogli bi dovesti do razumijevanja mehanizma tremora i konzekutivno tome do racionalnije terapije.

Tragovi metala koji mogu izazvati neravnotežu metabolizma amina u mozgu, mangan, aluminijum, bakar i željezo, ostali elektroliti, helati i metali i njihovo proučavanje — sve to može dovesti do eventualnog razumijevanja patogeneze tremora. Na koncu, Barbeau tvrdi da je tremor samo simptom a ne bolest, da danas bolje razumijemo tremor, njegovu patofiziologiju i etiologiju i da terapija amantadinom i L-DOPOM u nekim slučajevima ohrabruje.