SUMMARY OF SIMPOSIUM ON EPILEPSY

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The speakers in this Symposium have covered the subject in such detail and so critically, that a short summary is not possible; only some trends detected in the excellent presentations may be discussed. There is the impression that, although great advances have been made in the understanding of the basic mechanisms of epilepsy, the application of the laboratory discoveries to clinical problems has lagged behind tc a considerable extent. Several speakers admitted that our concepts of the subject and rationale for its treatment are not well established. Bay bemoaned "the great variety of nomenclature and great discord about classification". There are gaps in our knowledge of even the basic mechanisms for Ajmone-Marsan concluded "that essential essence of the epileptic disorder and the actual site and mode of epileptogenic agents are still poorly understood". Houston Merritt confessed "that we do not, as yet, have a rational form of medical therapy". Bengzon stated "we realize only too well how little we know about these drugs we use so often".

Basic mechanisms of epilepsy — The panel, chaired by dr. Jasper on the basic mechanisms of the epilepsies, emphasized the physiological pro-

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Nota do Editor — Uma das mais úteis sessões do Congresso Internacional de Ciências Neurológicas realizado recentemente em New York (21-27 de setembro, 1969) foi constituída pelo simpósio sôbre Epilepsias, no qual foram apresentados resultados de pesquisas feitas mediante tecnologia de alto padrão, discutidas interpretações visando a melhorar os conhecimentos sôbre as motivações das crises e expostas as vantagens e indicações das opções terapêuticas, médicas ou cirúrgicas, preventivas ou curativas. Certamente os trabalhos apresentados e as discussões que originaram serão compilados em volume que dentro em breve estará à disposição dos interessados. *Data venia*, ARQUIVOS DE NEURO-PSIQUIATRIA tem a primazia de publicar o resumo final dêsse simpósio, manuscrito por um de seus dois coordenadores (H. Houston Merritt e A. Earl Walker). Publicando-o sem tradução e dando-lhe o destaque de um trabalho original, pois que nesse "resumo" há muito da experiência do próprio autor, o Editor visou a chamar a atenção dos estudiosos para a importância dêsse simpósio para a sintetização dos conhecimentos atuais e como ponto de partida para novas pesquisas em Epileptologia e, ao mesmo tempo, prestar homenagem a A. Earl Walker, notável neurocirurgião que tem largamente contribuido para o melhor entrosamento das Ciências Neurológicas, procurando diminuir as barreiras entre os dados experimentais, as pesquisas neuroquímicas, as verificações eletrofisiológicas, os fatos observados clìnicamente e os resultados terapêuticos.

perties of the neurons and their environment particularly the cell membranes and their appendages. In this discussion problems relating to membrane polarization, inhibitory and excitatory, pre- and post-synaptic potentials, paroxysmal depolarization and hyperpolarization shifts were defined and their role in the epileptic process was suggested. These mechanisms relate to the individual neuron in the interictal state, when there are no overt manifestations of epilepsy. Dr. Marsan concluded that the behavior of individual elements between paroxysmal bursts does not differ in any notable way from that of the cells before the applications of the epileptogenic agent. Yet, from time to time the neuron will generate a spike but the membrane polarization keeps decreasing so that spikes are generated at a progressively higher frequency until a level of depolarization is reached at which spike generation ceases. This remains for 50-100 milliseconds and then the membrane repolarizes slowly but above the resting level, remaining there for several hundreds of milliseconds before falling to the original level.

Dr. Klee demonstrated that this high rate of firing was not due to a synaptic input. The essence of epileptic discharge is the synchronized firing of many neurons. Prince showed that such neuronal discharge was hemmed in by a surrounding zone of inhibition. However, cells responding to inhibitory impulses might, after a time, become involved in the burst discharge as it increased, and then as it subsided the cell again show an inhibitory response. This synchrony has been attributed to both release of inhibitory influences tending to confine discharges and the facilitation of excitatory elements. Structural connections at cellular levels have been implicated. However, the possibility exists that the synchronization of rapid firing may be related to glial participation in the discharge or to interaction between axons of a tract. It is known that the field effects modify the thresholds of excitability in peripheral nerves; such effects may be equally operative in the brain where many fibers are poorly myelinated or unmyelinated. Unison firing begins at the focus and propagates to secondary sites which discharge in time with the primary focus. As secondary and tertiary ganglia join in synchronous discharge, the pacemaker may shift from the original focus to secondary or tertiary points, where it continues to regulate spiking until termination of the seizure. The mechanisms involved not only in pacemaking but also in transfer are poorly understood. This shifting inter-relationship of primary, secondary and tertiary foci is of particular relevance to the more general control of cerebral activity by the reticular formation.

Because a simple cause-effect sequence cannot be found to explain the genesis of the epilepsy, many writers have assumed that several factors acted in combination to produce the epilepsy.

Clinical aspects — The probality of a multifactorial pathogenesis of the epilepsies was suggested by both Dr. Merritt and Dr. Bay. The strong hereditary trend in some forms suggests that genetic alterations might provide the background for secondary factors. Careful chromosomal studies might lead to promising approaches to the problem.

Epidemiological and demographic studies of epilepsy such as presented by Drs. Hendricksen and Krohn usually reveal interesting data. It is important to note that two-thirds of the epileptic population of Norway live a normal social and family life.

Our own studies of the lives of posttraumatic epileptics indicates that the majority of these victims are living a normal life — working and earning a livelihood, driving a car with a better accident and traffic record than the average person, marrying and enjoying connubial bliss to a greater extent than the average, if their divorce rate is a valid indication, and deficient only in life expectancy probably due to their brain damage.

Dr. Denis Williams emphasized the importance of the clinical study of patients and indicated the great number of technical examinations which may be made as part of the diagnostic workup. Rightly, he pointed out in his humorous style, that the practical value of the tests, which are often both timely and costly, should be considered. I fear that some of our younger physicians, so accustomed to requisiting all available special examinations do overtest to avoid the possibility of missing a surgical lesion. But, if the neurological examination, the spinal fluid, the EEG and the scan are normal, the chances of having missed a space-occupying lesion are less than 1% and little reduced by other tests.

The possible significance of febrile convulsions in the epilepsies was noted by several speakers. Dr. Frantzen and her associates found that 10% of children who had febrile seizures after 5-7 years had evidence of an organic behavioral disorder. Murray Falconer considered that febrile convulsions caused edema of the brain, tentorial herniation, medial temporal lobe sclerosis and psychomotor seizures. This interesting hypothesis would seem to explain the pathological changes seen in many ablated temporal lobes. However, a statistical analysis should be made to demonstrate that febrile seizures are a common finding in temporal lobe seizures.

Although methods of testing of new drugs are far from ideal, additional anticonvulsants continue to be added to the stock-in-trade medicines. Both Gastaut and Turner and his associates find that several new benzodiazepines are promising drugs against status epilepticus and certain chronic seizure disorders. Because these seem to be particularly effective in the Lennox-Gastaut syndrome and hypsarythmia — conditions for which our present anti-convulsants are not very satisfactory — they are especially welcome. That they may have suporific effects when given by mouth for some time, may not be as serious a defect as at first thought since many stimulant drugs are available.

Bengzon emphasized that although much of our epileptic therapy is empirical and trial-and-error, it is surprisingly good. More reliable results might come if the appropriate serum levels of the drugs were known, or if a simple technique were available for assaying the drug in the urine. By such controls, interference phenomena washing out of the drug by systemic disorders might be detected early. Whereas, now we watch the hematopoietic system for toxic effects, perhaps other tests for impairment of mentation, alteration of personality etc., should be routine.

Pathology of epilepsy — Dr. Seitelberger has very clearly brought out the dilemma of the neuro-pathologist who examines the brains of epileptics and non-epileptics. The pathological lesions clearly seen in the brain even when examined with the highest powered lens have no pathognomic characteristics of epilepsy, so that their causal relationship to the seizures becomes more of a philosophical than a scientific question. Dr. Seitelberger points out that the factor common to most epilepsies is the scarring — either connective tissue or glial which occurs in the brain.

Certainly the majority of the brains of people with acquired epilepsy have some connective tissue and/or glial scars with blood vessel proliferation. Except for morphological descriptions of the areas, little attention has been paid to their dynamic and biochemical properties. Yet, if they behave as other scars, their presence should produce marked alterations in the energy dependent transport systems of the brain. Little is known of the enzyme activity of new vessels and of their ability to pass oxygen, glucose and electrolytes in a form available to the cells either in early or late stages of cicatrization. One might assume that as the scar contracts, such vessels would lose their ability to transport molecules and ions across their endothelium. In addition decreased flow might impair thermo-regulation of the area and interfere with activities of thermosensitive enzymes. Under normal circumstances, even an augmented blood flow as a cortical seizure develops, is unable to carry off heat developed by energy systems so that the local temperature rises. With impaired vascular responses this hyperpyrexia may be greatly increased.

The progressive gliosis in the scarred area may well modify the local metabolism and, in fact, may be an adaptive response to a decreasing amount of available energy sources. Metabolic properties of such glia may be determined by such techniques as Cartesian diver micro-respirometry and enzyme assays of sub-microgram samples.

The few electron microscopic observations of reparative processes on neuronal membrane suggest that following injury, there is complete disruption of the terminating boutons with replacement of many by glial, probably astrocytic, processes. The effect of such changes on the enzyme systems related to membrane permeability is unknown. A study of enzyme changes as a cerebral scar develops and matures, might give considerable insight into the basic processes which predispose a neuron to hyperactivity. Such an investigation should include not only the enzymes required for energy but the turnover of the more permanent constituents of the cells. For genesis of an epilepsy, changes in the latter might be particularly important. One would be especially interested in the activity of the cells which at the site of their traumatically disrupted axones had developed terminal balls. Do such cells maintain functional connections in cortex or subcortical structures?

Finally, normal transport of degradation products and water to capillaries and to the ependyma may well be severely impeded by the scar.

Surgery for epilepsy — The surgical therapy of epilepsy Dr. Ward stated was applicable to only a small percentage of epileptics — perhaps

5%. When all criteria for operation are met, the results are good. Although Dr. Rasmussen emphasized that the removal of epileptogenic tissue is the goal of the surgeon, one cannot help but wonder, when essentially similar results are obtained by many different techniques, if more basic factors might not be involved. The observations made with depth electrodes as Bancaud described certainly indicate that the mechanisms are complex.

The use of depth recording in the study of a patient with a possible focal epilepsy was discussed briefly by Dr. Bancaud. These records made from multi-electrode probes stereotactically inserted into the subcortical cerebral ganglia, particularly the frontal and medial structures, allow well-controlled studies to be made of both spontaneous and electrically induced activity. They may serve a number of purposes: 1) A diagnostic aid; 2) The lateralization of an epileptic foci; 3) The localization of an epileptic focus; 4) The identification of subcortical area at the tip of the electrode by recording and stimulation; 5) Polarographic recording. Using noble metal electrodes, Grey, Walter, Ray and others have shown that polarographic tracings may be made for oxygen, hydrogen and other ionic concentrations in the tissue.

Impedance measurements may also enable one to determine boundaries of tissues within the nervous system and allow one to evaluate the responsiveness of specific structures to different types of behavioral, electrical and pharmaceutical transients. Such technique may allow one to delimit the extent of a subcortical softening or tumor. The potentiality for such subcortical polarization methods are quite great and when combined with a directly coupled computer, may enable the diagnostician to make rapid comparative decisions of many physiological variables and thus establish those criteria, diagnostic of specific disease entities. As a bi-product of the depth stimulation, psychological studies may be made of transient localized disturbances.

The chronic implantation of electrodes has allowed stimulation of these subcortical structures under well controlled psychological conditions. Observations of the effect of spontaneous and induced discharges on memory and behavior have been made in several centers. Drs. Chapanis, Laws and Blumer have studied the effects of stimulation of subcortical centers upon mentation.

The psychological testing is carried out concurrently with the EEG evaluation in the same room with the patient. The psychologist is unaware of the particular order of stimulation in any given session, but knows that for each psychological task, a series of base-line control items precedes the stimulation, followed by two task items for every stimulation.

Initially we tried to test two kinds of verbal memory — old learning and new learning using for this task familiar and novel nursery rhymes. Occasionally, the patient would respond with parts of the sentence correct and parts quite wild. The patient, however, would monitor what he said and be disconcerted if he realized his response didn't make sense. To

avoid this feedback, we tried non-sensical sentences which learning theorists have been using for a number of years to study the structure of language. In this way, the patient would be able to say whatever he "remembers" without noticing the intrusion of foreign material. Here is an example of a nonsense paragraph: "A school is very trying circumstances and are such truths as all the football has a new instrument has a person is very enjoyable is a fine way to open one's wallet..."

The nonsense sentences represent new learning; old learning ways may be tested by analyzing the associative structure of the patient's own language that is, his word associations (Word Association Norms, 1964). Instead of asking for one association, however, we asked for three successive associations to the same word. These words were arranged in sets of about the same associative strenght. By using words for which population norms were available, we hope to be able to score objectively for deviancy of reponse.

The best way of illustrating the psychological information gained from such depth electrode stimulations is to consider one patient (G.J.) who suffered epilepsy as the result of an automobile accident which damaged the right frontal lobe. This patient was tested on 10 successive days, using four forms of nonsense sentences and 5 lists of word associations. The results were analysed using the Chi-square and "variance" techniques. Intruded foreign words come exclusively after stimulation in the right amygdala for this patient. Extra response words come primarily on stimulation in the left amygdala and after a short delay, in the right amygdala. The right hemisphere produces a delay in the reaction time, and it is primarily the deepest right frontal area that is involved. The EEG recordings on stimulation showed a great deal of spiking in the deep right frontal leads, and some spiking in the right amygdala.

Berger's hopes that psychophysiological correlations might be made with his brain waves, seems possible from such studies of mentation and memory promise to reveal some of the psychic abnormalities associated with epileptic patients.

The results of surgical therapy, irrespective of the type of operation are surprisingly good, and the surgical procedures carry little risk.

The Russian surgical experience was similar to that reported by Falconer from England and Rasmussen from Canada. Although the relief of seizures after amygdalotomy as reported by Narabayashi from Japan and Haton and Udom from Thailand, was not as great as that following temporal lobectomy, approximately 30% of the patients were greatly improved. Both authors emphasize that behavioral disturbances, especially aggression, were much diminished.

Final comments — Perhaps it is appropriate to conclude this summary by an inquiry into the mysteries which remain. The clinician has difficulty explaining a number of phenomena associated with seizures. The first is why one patient suffering from a certain condition has a seizure,

whereas, another with the same disorder does not. The second concerns the periodicity or intermittency of attacks. The third relates to the seizure pattern be it focal or generalized, and as a corrollary, why is it different in neonatal and adult life. The fourth inquires into factors which initiate seizures after a head injury and those responsible for their recession some years later. Finally, clinicians would like to know the teleological significance of seizures. These are some questions to which future investigation might be directed.

Although it is true, as Dr. Merritt said, that there are many gaps in our knowledge of epilepsy, nevertheless, we now have the instrumentation to examine and assess with precision, the characteristics of the epilepsies. It would seem that by carefully planning our research designs and using the instrumentation at hand, that we could provide answers to most of these questions. But, that will require time so that we must await another Congress to resolve these mysteries.